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THE HEART MUSCLE IN TYPHOID FEVER

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INTRODUCTION

Some years ago, following a suggestion made by Dr W S Thayer, I undertook to study the condition of the heart muscle of patients who had died of typhoid fever in the Johns Hopkins Hospital It has long been a custom in the pathological department to save portions of the organs from all autopsies Such portions have been hardened in Muller's or Zenker's fluid and preserved in alcohol With the consent of Dr Welch this material was placed at my disposal From the autopsy records I selected for study fifty consecutive cases of death during typhoid fever In seven instances no heart muscle had been preserved, so that the number to be studied was reduced to forty-three The portion of the heart muscle found consisted of one or more strips from the left ventricle From various portions of these strips, small blocks were cut and imbedded in celloidin or paraffin The sections were for the most part stained in hematoxylin and eosin, although carmin and Van Gieson's stain were also used The number of blocks to a given case varied from two to ten In all, sections from 197 blocks were studied The clinical features of each case were ascertained from the medical records, which are unusually full The general autopsy findings were readily available in the fasciculi of the pathological department

I have realized from the beginning how incomplete the conclusions based on such fragmentary evidence must be From small bits of the left ventricle one is not justified in drawing conclusions about the heart as a whole If a lesion is present it may be isolated, if it is absent it may exist in other parts of the heart Only some method such as Krehl's,[1] in which the whole organ is cut into small blocks and sections from each studied, can be considered thorough It is noteworthy, however, that in cases in which a lesion of any extent and particularly an interstitial lesion was found, it was present in all of the slides from that particular case and in cases in which no marked changes existed, none of the slides have shown them It is quite true that some portions of the heart muscle show lesions more extensively than others and the variation in

1 Krehl Deutsch Arch f klin Med 1890, xlvi 484

this respect may introduce a serious error of judgment The work, however is presented with this deficiency clearly in mind I merely hope that in a general way it may emphasize an important lesion of typhoid fever and show its relation to equally important and interesting clinical symptoms

HISTORICAL REVIEW

The condition of the heart in typhoid fever was first commented on in the early part of the last century and studied with care twenty and thirty years ago At that time it attracted considerable interest and received its fair share of literary attention Its importance was fully realized and little has been added to what was then written about it With the rather general abandonment of morphological investigation due to the exhaustion of the possibilities of existing methods, this field has lost its attraction In the literature of the past ten years scarcely an article of importance has appeared and one will search the *Index Medicus* for the past five years in vain Laennec[2] and after him Louis[3] speak of the softness of the heart muscle in typhoid fever and of the yellowish mottled coloring—the dead-leaf appearance Louis compared it to a wet cloth which will retain any form into which it may be pressed He makes these lesions the explanation of certain changes observed in the pulse, an association already guessed at by Laennec Stokes[4] in his book on the heart, published in 1854 gives a much fuller description of the changes than Louis did and points their relation to clinical symptoms with more precision Virchow,[5] in 1852 gave an accurate description of the microscopical fiber changes which he considered inflammatory and his views were elaborated by Bottcher[6] The first extensive and complete consideration of the subject is by Havem[7] in 1869 In a study of four cases of typhoid fever with sudden death he describes in detail the fiber lesions and for the first time draws attention to the interstitial changes which in subsequent contributions assume so much importance He lays great emphasis too on changes in the coronary arteries notably a wide-spread endarteritis of the small vessels which he considers the direct cause of

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2 Laennec Traité de l'auscultation médiate Paris 1879 p 815

3 Louis Researches on Typhoid Fever Transl by Bowditch Boston 1836, p 28

4 Stokes Diseases of the Heart and the Aorta Dublin 1854

5 Virchow Virch Arch f path Anat 1852 iv 261

6 Böttcher Ueber Entzündung und Zerfall der Muskelfasern Virchow's Arch f path Anat 1858 xiii 249

7 Havem [illegible] Arch d phys norm et path 1869

death His observations were preceded by the notable contribution of Zenker[8] on the lesions of the voluntary muscles in typhoid fever Zenker had noted in one of his cases extensive granular degeneration of the heart muscle Following Hayem's paper there appeared a large number of publications on sudden death in typhoid fever and the concomitant heart changes A clinical type was set up, described as the "forme cardiaque de la fièvre typhoide" The most notable contributions are from Hayem,[9] Huchard,[10] Landouzy and Siredey,[11] Déjerine[12] and Willaume[13] In Germany the studies of Birch-Hirschfeld[14] and Leyden[15] on diphtheria myocarditis extended the knowledge of interstitial lesions In 1891 Ernst Romberg[16] published a most complete review of heart changes in typhoid fever, scarlet fever and diphtheria In a careful study of 11 hearts from patients dying of typhoid fever he noted granular degeneration marked in 3 and moderate in 7, fatty degeneration marked in 2, moderate in 4 and absent in 5, hyalin degeneration slight in 2 and absent in 9 Segmentation was common Many fibers showed vacuolar degeneration and, on cross-section, increase in the sarcoplasm Nuclear changes were marked but not as extensive as in diphtheria Interstitial infiltration he found marked in 2 instances, moderate in 3, slight in 1 and absent in 5 In a very suggestive way he brings these lesions into relation with the circulatory symptoms observed during life Picot[17] has substantiated Romberg's findings and nothing of importance has been added to the subject since then

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8 Zenker Ueber die Veränderungen der willkürlichen Muskeln im Typhus abdominalis, Leipsic, 1864

9 Hayem Des manifestations cardiaques de la fièvre typhoide, Progrès méd, 1875, Quoted by Renaut Cong franç de méd, 1899, II 1

10 Huchard Etude critique sur la pathogénie de la mort subite dans la fièvre typhoide Union méd, 1877 Quoted by Renaut Cong franç de méd, 1899

11 Landouzy and Siredey Etudes sur les localisations angio cardiaques typhoidiques leurs consequences immédiates, prochaines et éloignées Rev de méd 1887, VII 804

12 Déjerine Sur les altérations du myocarde comme cause de mort subite dans la fièvre typhoide Soc de biol December, 1885 Quoted by Renaut

13 Willaume De la forme cardiaque de la fièvre typhoide, Thèse de Nancy 1887

14 Birch Hirschfeld Quoted by Romberg, Deutsch Arch f klin méd, 1891, XLVIII 369

15 Leyden Ueber die Herzaffectionen bei der Diphtherie Ztschr f klin Med, 1882 IV 334

16 Romberg Ueber die Erkrankungen des Herzmuskels bei Typhus abdominalis Scharlach und Diphtherie Deutsch Arch f klin Med 1891 XLVIII 369

17 Picot Semaine méd 1894 XIV 57

THE ANATOMICAL LESIONS OF THE HEART MUSCLE IN TYPHOID FEVER

It is difficult to make any detailed classification of the gross cardiac lesions described in the pathological records, but certain almost constant findings stand out prominently The effects of granular and fatty degeneration are particularly striking In nearly all instances the muscle is described as paler than normal and soft in consistency In one instance the note is made that the ventricle walls retain the impression of the fingers wherever they are pressed, in another, that the heart collapses over the hand The color is variously described as brownish-red, light brown, etc., but gray and yellow predominate In appearance it is nearly always described as opaque or cloudy or as showing the mottling characteristic of fatty degeneration Small hemorrhages are frequently noted

Fig 1.—Series 9 marked degeneration and atrophy of muscle fibers

and in a few instances grayish or yellowish areas characteristic of foci of interstitial infiltration or complete fiber degeneration In only seven instances is the muscle described as firm and little altered in appearance Fresh sclerosis of the aorta and coronaries was noted eight times and as all but one of these observations were made at recent autopsies it is probable that the lesion has occurred more commonly than described

For descriptive purposes it is convenient to divide the histological changes into fiber lesions interstitial lesions and vascular lesions

The most common changes that one finds in the muscle fibers of the heart in acute infectious diseases namely granular and fatty degeneration are not very evident in the sections studied The hardening and

preservation of the tissue would, of course, remove any fat that may have been present and obscure the albuminous granules Such pictures of granular degeneration as one sees in fresh specimens have never been encountered Still, many of the fibers show a well-marked granular appearance It is the granular degeneration that makes the striation appear indistinct in many fibers In only one instance were fibers seen that seemed to have undergone hyaline degeneration, and these *en masse* in a single area Amyloid degeneration was not observed

Fig 2—Series 9, degenerated muscle fibers with large vacuoles

Many of the fibers show a distinct loss of striation although marked alterations were noted in only four instances The transverse bands are affected more frequently than the longitudinal At times large vacuoles are noted in the fibers often traversed by indistinct striæ Occasionally a whole fiber is degenerated and filled with these irregular vacuoles

In one instance there seems to be a wide-spread atrophy of the muscle cells a lesion to which Diago[18] particularly has called attention The

[18] Diago Beiträge zur Histopathologie des Typhusherzens Beitr z path Anat zu allg Path 1901 xxix 142

muscle bundles are widely separated and between the shrunken individual fibers are large interspaces filled with a coagulated serous fluid studded with a few connective tissue cells and a few leucocytes Vacant spaces show where fibers have completely disappeared (Fig 1)

On cross-section changes are often still more evident The fibril bundles are small and widely separated Their number is frequently decreased and a large area of the heart muscle may be composed of fibers with only a peripheral zone of fibril bundles somewhat resembling, under

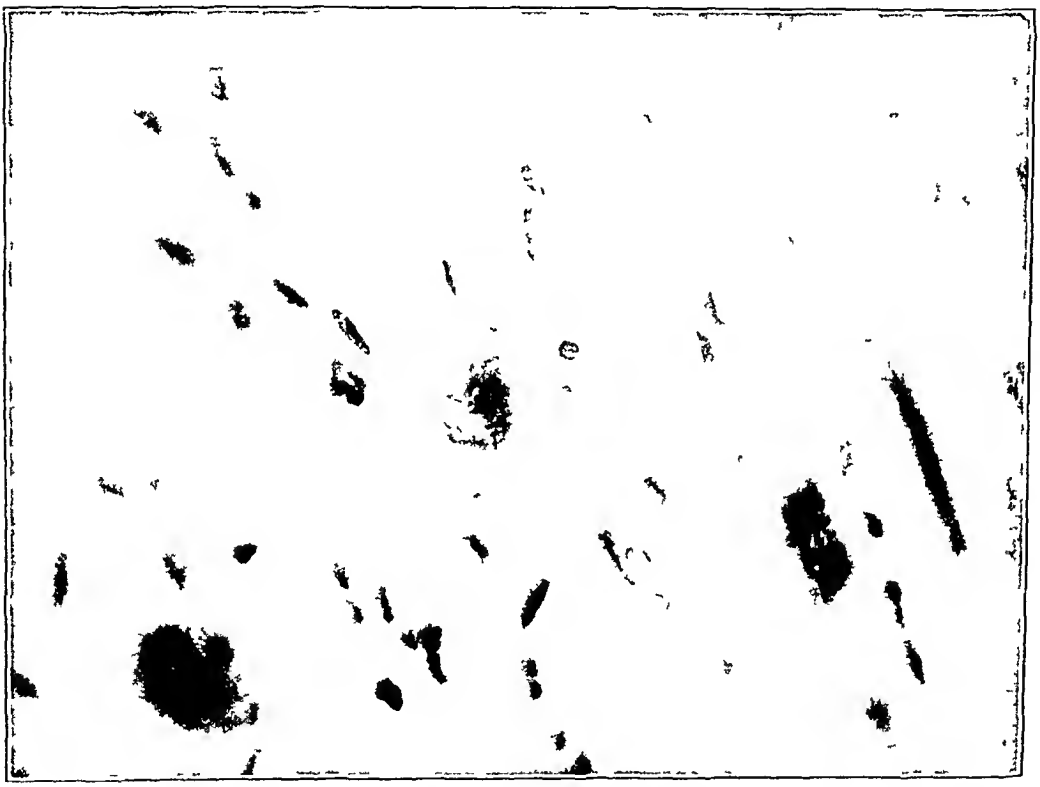

Fig 3—Series 9 Large vesicular nuclei From photomicrograph by Dr M C Winternitz

the low power adipose tissue Vacuolization is particularly well seen in some instances (Fig 2) Krehl suggested that these vacuoles were spaces from which fat had been dissolved There is however nothing to support such a view and it has been discarded

Fragmentation is one of the commonest of the lesions It was present in twenty-five instances and extensive in eleven It varies from an

unusual distinctness of the "cement lines" to complete separation of the fibers, often with dislocation [19]

The most constant of all the fiber lesions are changes in the nuclei Not a single specimen but shows them to some degree, and in thirty-two instances they were well marked The perinuclear spaces are enlarged and there is an accumulation of pigment granules at the poles Frequently two nuclei lie side by side and occasionally in such a manner as to suggest division The nuclei themselves show most far-reaching changes They are swollen, often to four or five times their usual dimension, are vesicular and filled with a few irregular strands of chromatin Many look like empty pouches and others show the most irregular and bizarre outlines (Fig 3)

The interstitial changes have particularly attracted my attention Well-marked interstitial edema was noted in eight cases and extensive hemorrhages in six In about one-half of the cases there is a noticeable increase in the cells in the interstitial tissue These consist of scattered small mononuclear cells and some large mononuclears and an occasional polymorphonuclear The cells are grouped principally about the blood-vessels Of more importance are the focal accumulations of cells first described by Havem and later emphasized by Romberg These foci may as Ribbert[20] claims be divided into two types The foci of the first type consist almost entirely of small round cells and resemble lymphoid nodules Ribbert, indeed believes that they represent hypertrophy of normal lymphoid structures They are found principally under the epicardium and occasionally under the endocardium In some cases they form an almost continuous band under the epicardium with here and there nodular enlargements More commonly they are small groups of cells which show little tendency to dip down between the muscle bundles, although in the papillary muscles limited invasion is sometimes seen Exceptionally similar nodules occur in the connective tissue spaces between the muscle bundles

The second type of cellular accumulation is more intense and extensive In different specimens the kind of cell and the relative proportion

19 Newer anatomical studies have demonstrated that the cardiac musculature is a syncytial tissue and is not divided into distinct cells The cement lines which were formerly regarded as marking the outlines of the cell and being the point of contact of adjoining cells are areas of irregular contraction They have the same significance as fragmentation See Aschoff and Tawara Die heutige Lehre von dem pathologisch anatomischen Grundlagen der Herzschwäche Jena 1906

20 Ribbert Ueber Myocarderkrankungen nach Diphtherie Mitt a d Grenzgeb d Med u Chir 1900 v 1

of the different cells vary Most commonly the small round cell predominates with a liberal interspersing of large mononuclear cells and some polymorphonucleais All the areas contain, too, certain large endothe-

Fig 4—Series 27 an area of infiltration consisting almost entirely of large cells with oval eccentric nuclei

lioid cells with round or oval eccentrically placed nuclei A few of these cells had acted as phagocytes In one instance they were the predominating indeed almost the only type of cell present (Fig 4) In another

instance there is an astonishingly large number of eosinophils (Fig 5) These cell accumulations arise frequently beneath the epicardium or endocardium and dip deeply down into the muscle running irregularly between the bundles and along the course of the blood-vessels (Figs 6 to 10) Others occur as foci within the muscle itself when their relation to the blood-vessels is particularly striking In nearly all instances they arise

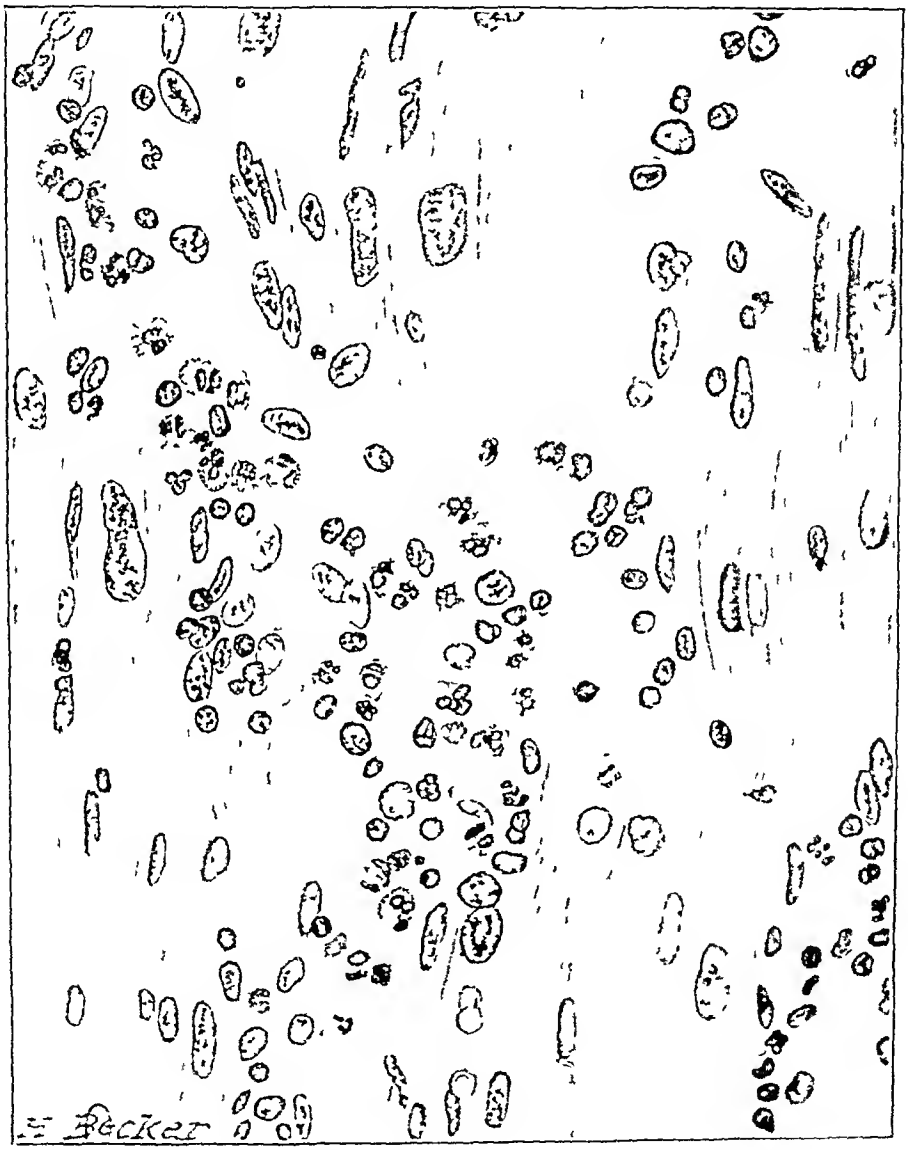

Fig 5—Series 31 the large number of eosinophils is noteworthy

in the connective tissue bands about a medium-sized vessel and from this base pierce irregularly between the muscle bundles and cells I have looked particularly to ascertain the relation of these bands of cellular infiltration to degeneration of the muscle cells I may say confident that they are not limited to areas where the fiber changes are most se-

ing, and, indeed, seem to bear no definite relation to the fiber lesions The papillary muscles are a favorite site for these interstitial changes, although as a rule they are not most extensive there Such interstitial cellular accumulations were observed in twenty-nine cases and in fifteen they were rather intense and extensive In many sections showing the presence of old chronic fibroid lesions these areas are the seat too of an acute inflammatory reaction The bundles of degenerated fibers and the fibrous tissue itself are surrounded and infiltrated by leucocytes and red blood corpuscles

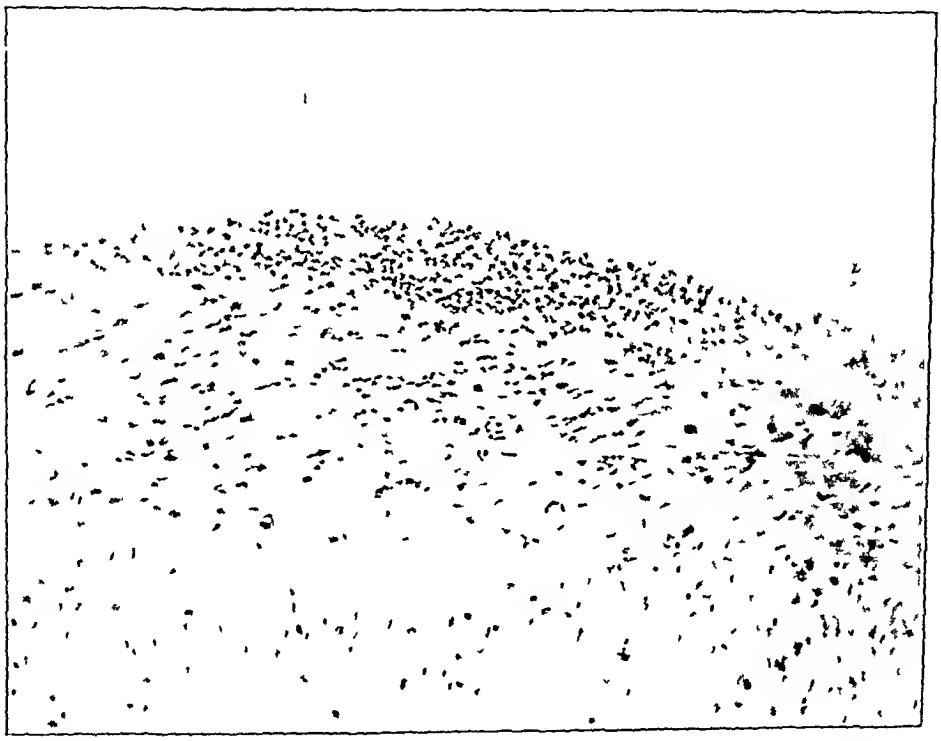

Fig 6—Series 5, area of filtration in and under the endocardium with some invasion between muscle fibers The cells consist of small and large mononuclears with many of the large cells with eccentrically placed nuclei and homogenous eosin staining protoplasm From photomicrograph by Dr M C Winternitz

The blood-vessels in most sections are unusually full The capillaries stand out prominently and are engorged Some of the larger vessels in the pericardium show an acute periarteritis (Fig 11) In five cases there is a definite endarteritis in the coronary arteries and this lesion would undoubtedly have been more frequently found had more sections included portions of the coronaries Nothing in any way approaching

the extensive endarteritis in the small vessels described by Hayem was observed Occasionally the endothelial cells appear swollen and there is a slight accumulation of round cells in the media

THE PATHOGENESIS OF THE HEART MUSCLE LESIONS

Renaut,[21] following the experimental work done in his laboratory by Mollard and Regaud,[22] gives a simple explanation of the sequence of

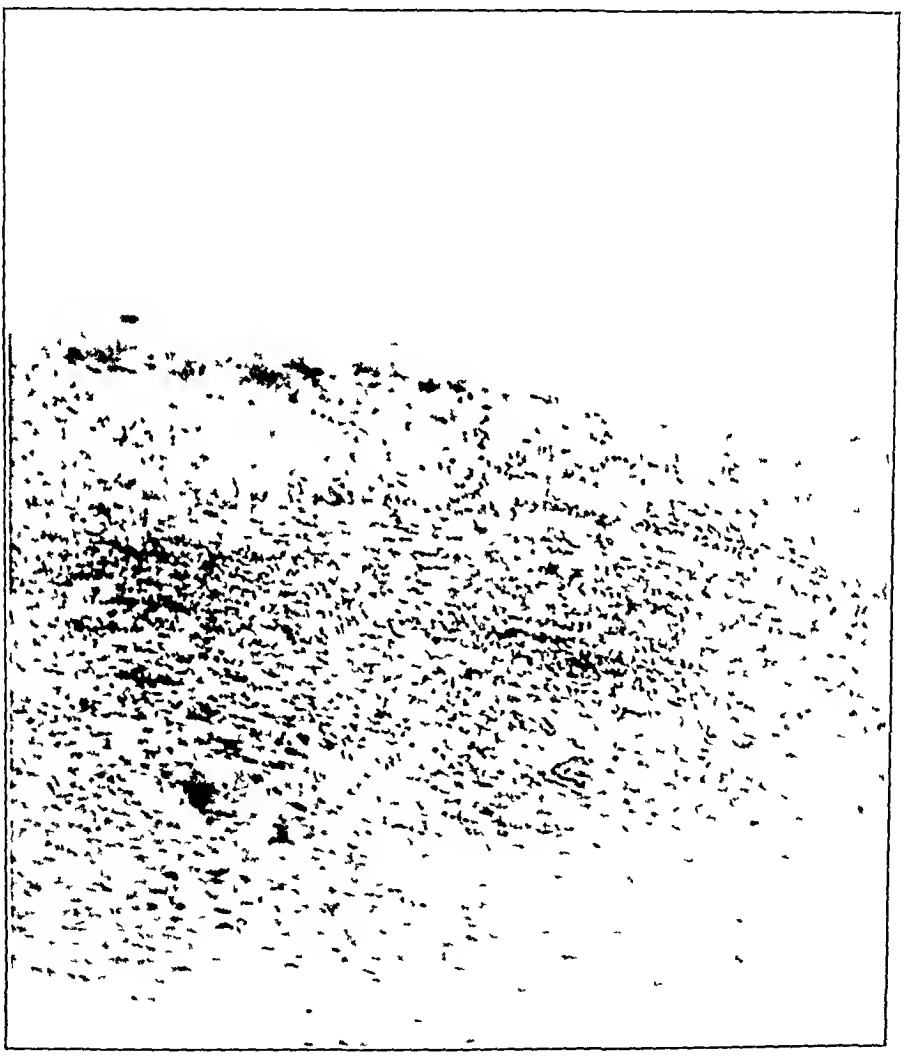

Fig 7—Series 31 area of extensive infiltration under the epicardium These are marked areas of hemorrhage The small mononuclear cells predominate but there are many large mononuclears and a few large endothelioid cells Eosinophils are particularly abundant (Specimen from same case as Fig 5) From photomicrograph by Dr M C Winternitz

21 Renaut Les myocardites aigues Cong franc de med 1899 p 1

22 Mollard and Regaud Contribution à l'etude expérimentale des myocardites, Ann de l'Inst Pasteur 1897, xi 97

events in the myocardial lesions of acute infectious diseases Although the work of Mollaid and Regaud was performed with diphtheria toxin the lesions produced are so similar to those of typhoid fever that the principles established for one might be readily applicable to the other The changes are divided into four stages

1 The lesions of attack These are the immediate results of the action of the toxin They occur only in the muscle fibers and may be the sole change when death follows quickly The lesion consists of granu-

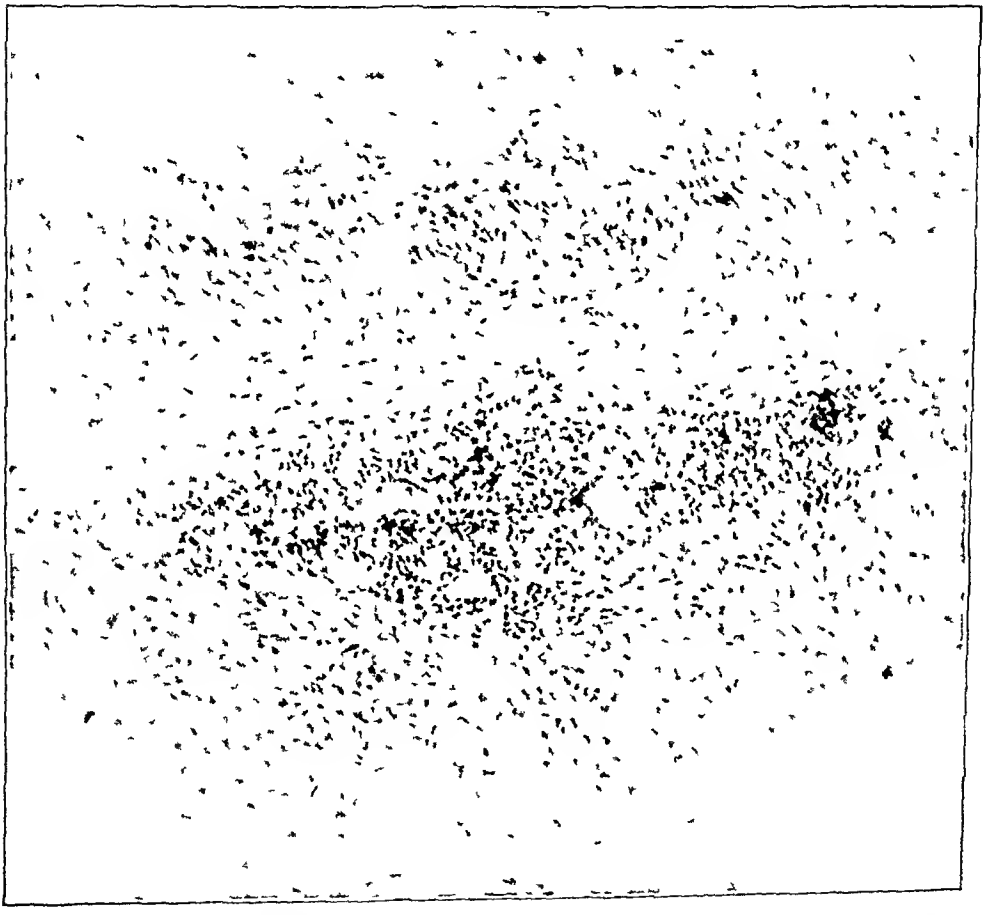

Fig 8—Series 9 an area of infiltration beginning under the epicardium and infiltrating the muscle Although there are many small mononuclear cells, they are surrounded by an unusually rich zone of cell protoplasm Many large mononuclear cells with vesicular nuclei An occasional pus cell From photomicrograph by Dr M C Winternitz

lar degeneration followed by a more uniform staining with eosin and disappearance of cross-striation On transverse section the fields of Cohnheim are diminished in size and later disappear leaving a homogeneous appearance There may be a general hyperemia vascu-

2 The defense reaction of the heart cells Cohnheim's fields become still more obscured and the spaces between the cylinders of Leydig enlarged The fibers become vacuolar and this change is followed by an extensive fatty degeneration There is a marked increase in the amount of sarcoplasm which may exude into the interspace between the cells Nuclear changes are common and segmentation and fragmentation frequently occur

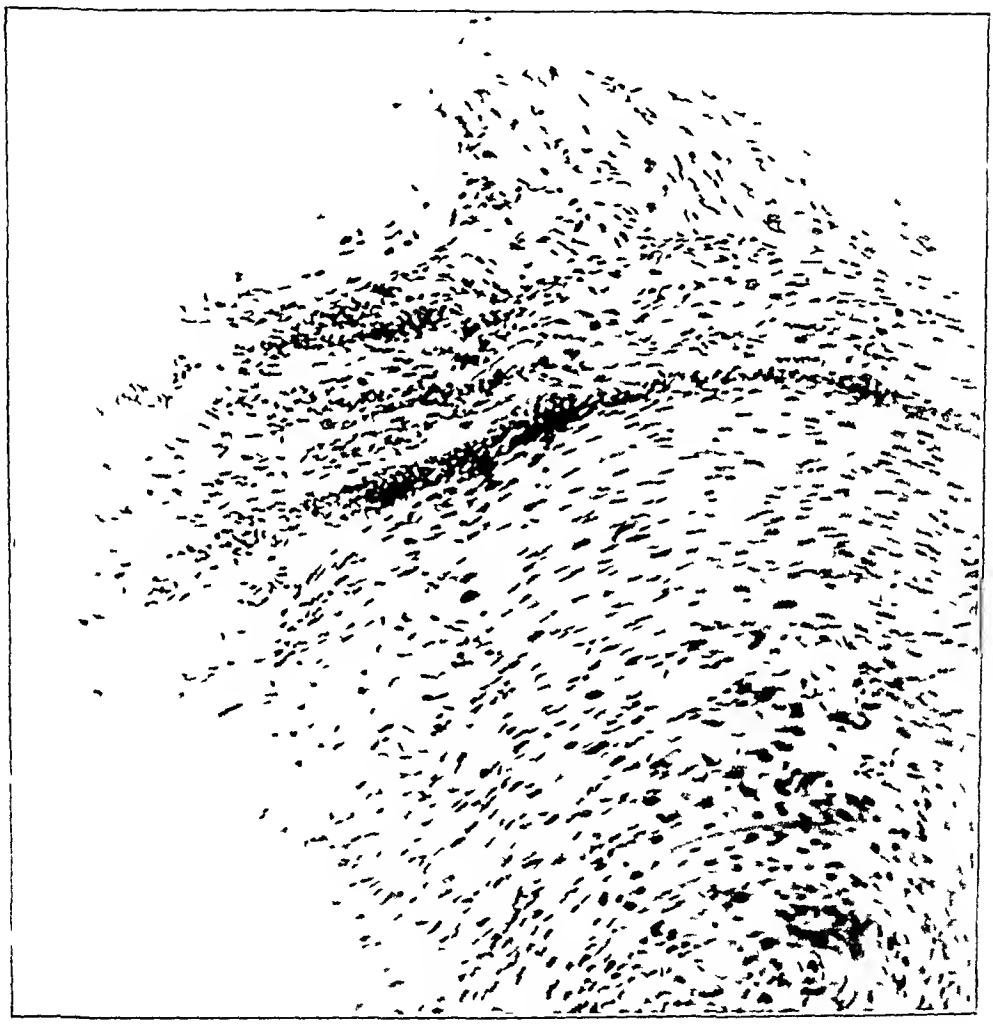

Fig 9—Series 43, area of extensive infiltration in a papillary muscle Character of cells about same as in previous figures From photomicrograph by Dr M C Winternitz

3 Liquidation of the muscle fibers Up to this time there has been only an increase of the small mononuclear cells in the blood-vessels themselves There is now a general pouring out of leukocytes about the dying cells which then rapidly undergo solution

4 With the disappearance of the leukocytes, fibrous tissue is formed and months afterward a scar is left as the result of the primary damage to the muscle fibers

The damage to the muscle cell is then the first and the essential cardiac lesion of infectious diseases and the interstitial changes are merely consequent on this Renaut rejects any idea of a primary interstitial inflammation He lays great emphasis on the fact that Mollard and Regaud find that areas of interstitial infiltration never occur before the twelfth day This fits well into his view He comments, too, that

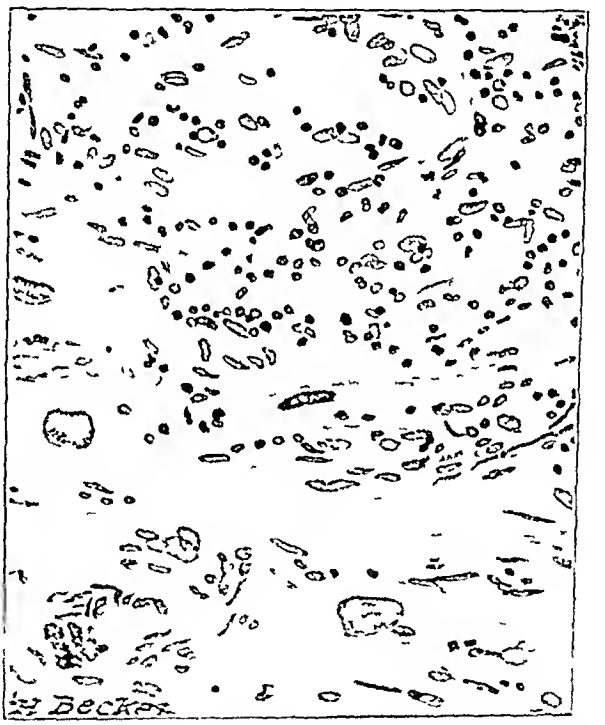

Fig 10—Series 31 an area of infiltration under the epicardium showing the usual type of infiltrating cells

we never see a pure interstitial myocarditis while changes in the fibers alone occur frequently

The histological picture of the hearts I have studied does not support this simple explanation of Renaut's As Romberg has pointed out and Krehl[23] has emphasized the areas of interstitial infiltration bear no direct relation to the fiber lesions They are by no means most marked where the fiber changes are severest and frequently surround healthy muscle cells Their intimate relation to the blood-vessels as previously com-

23 Krehl Erkrankungen des Herzmuskels Nothnagel's System 1901 p 287

mented on, is a much more striking association It seems scarcely possible that their extravasation could be directly due to an attraction offered by the dying muscle cells That they occur later than the fiber lesions is no direct proof of their secondary nature

THE CIRCULATORY SYMPTOMS OF TYPHOID FEVER

In studying the clinical records of my cases only the unusual circulatory symptoms have been selected The changes in rate and pressure and the general phenomena of failing circulation which appear before

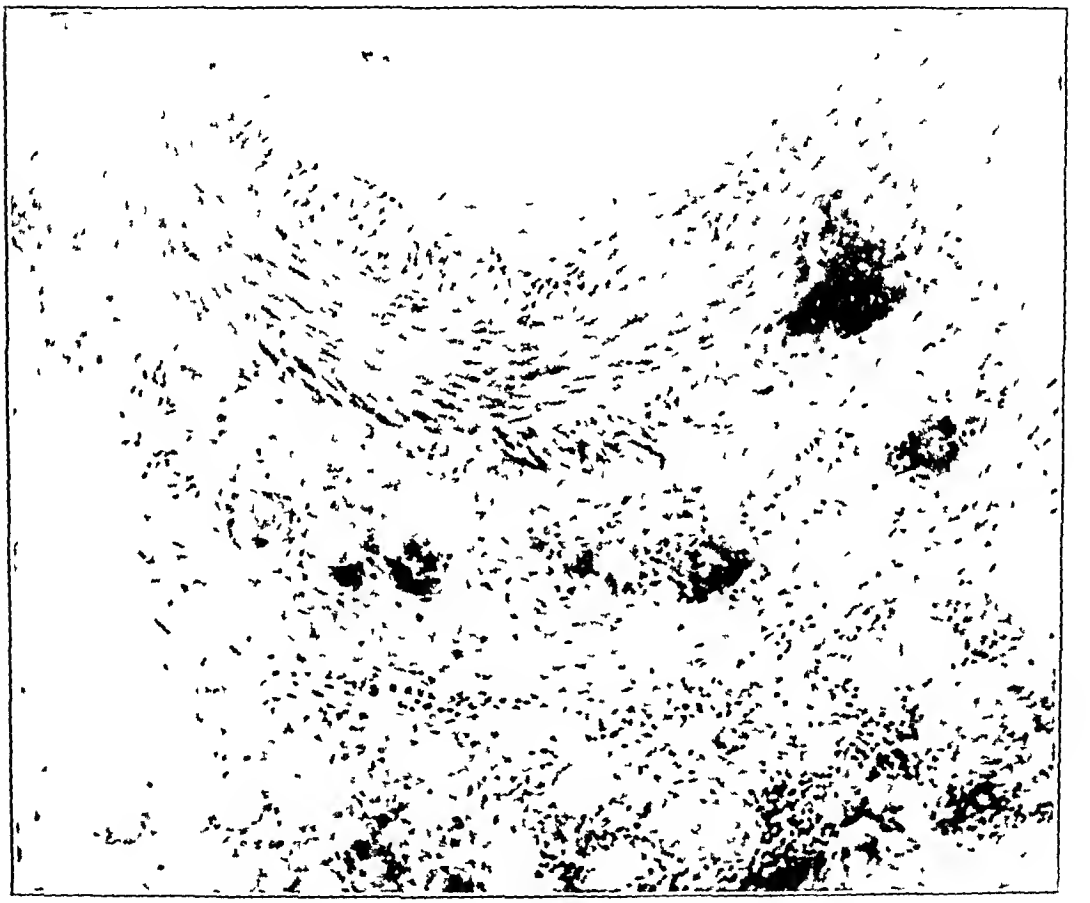

Fig 11—Series 9 perivitentis of the coronary artery From photomicrograph by Dr M C Winternitz

death and are common to all infections have not been regarded What I have sought for particularly are those symptoms which for days and even weeks lead one to assume the presence of cardiac damage and to

24 The circulatory symptoms of 1458 cases of typhoid fever studied in the wards of the Johns Hopkins Hospital have been carefully analyzed by Thayer On the Cardiac and Vascular Complications and Sequels of Typhoid Fever Bull Johns Hopkins Hosp 1904 xv 322

anticipate a fatal termination Such circulatory symptoms are far less prominent in typhoid fever than in diphtheria or scarlet fever Still at least in my fatal cases, they are by no means uncommon It may be said that in the routine observation of our patients no unusual diagnostic *finesse* has been directed to the condition of the heart and circulation

Of the forty-three cases studied the clinical records of two have been lost Of the remaining forty-one cases eleven showed prominent circulatory symptoms, twelve less marked but definite circulatory symptoms and eighteen no unusual circulatory symptoms

Five patients had a pulse-rate unusually rapid and out of all proportion to the temperature and general symptoms Huchard begins his book on diseases of the heart with the description of a typhoid patient with this symptom and emphasizes its grave significance The pulse was unusually slow and irregular in one case In sixteen instances there was irregularity varying from an occasional extrasystole to marked irregularity in force and rhythm Two cases were noteworthy for rapid changes in the quality and rate of the pulse I lay no emphasis on a small, low-tension pulse because these changes are more probably due to abnormalities in the vasomotor control than to cardiac changes

In three cases the first sound is described as approaching the second in quality and the intervals between the two sounds as of even duration

Two cases showed marked gallop rhythm and three embryocardia The heart sounds are described as feeble and muffled in four cases The first sound at the apex as unusually feeble twice, as of a murmurish quality twice, as of an indefinite quality once and markedly reduplicated twice A blowing systolic murmur was heard at the apex in eight cases In six it was present on admission, the patients being admitted on the fifth eleventh, (two cases), fourteenth, sixteenth and forty-second day of the illness, in two of these it was absent upon subsequent examination In two instances the systolic murmur developed while the patients were under observation The second pulmonic sound was markedly accentuated in four instances

One patient had marked dyspnea but at autopsy there was edema of the lungs and pleural effusion

These are in the main the symptoms that are usually described Huchard lays particular emphasis on the ominous significance of embryocardia The tendency of the two sounds to approach one another in quality and of the intervals to become more nearly equal is the first stage of approaching embryocardia The feeble indefinite first sound at the apex is the beginning of the development of a systolic murmur

More than one of these symptoms were present in many cases and indeed in a few the circulatory symptoms were so prominent that they may well be classed in the "forme cardiaque" of typhoid fever described by the French authors Two very characteristic cases are the following

FIRST CASE

Series No 9 Medical No 16215 Male medical student aged 25, white, American, admitted to the Hospital Oct 2, 1903, died Oct 15, 1903

Present Illness—The patient was brought to the hospital in a very collapsed condition, was deeply intoxicated and very dull No definite history of his illness could be obtained Patient had left home for college on September 14, and was then not in his usual spirits, apparently not very well He returned to the city on October 1 in a very exhausted condition, with high fever and delirium No detailed account of the symptoms during the preceding two weeks could be obtained After reaching home he was put to bed, and typhoid fever was diagnosed by the family physician from a positive Widal reaction The following note was made on October 3 by Dr McCrea

Examination—"Patient looks deeply intoxicated, mental condition dull, and at times some wandering Tongue dry Mucous membranes good color Slight tremor of lips Percussion note clear throughout, rather hyperresonant Breath sounds everywhere heard, accompanied by medium dry râles Point of maximum impulse in the fifth interspace Relative cardiac dulness begins at third rib, does not go to right of sternum Heart sounds clear throughout, first sound much like second Pulse 30 to the quarter, fair volume, markedly dicrotic, right larger than the left Abdomen is natural Numerous rose spots Respiratory movements well marked Walls soft and no tenderness On attempting to feel the spleen there is some rigidity, although spleen is palpable Relative hepatic dulness begins at the sixth rib and extends 11 5 cm in the right mammary line" Hemoglobin 80 per cent , leukocytes 5,000

Course of Disease—October 4 Note by Dr McCrea "Active delirium still continues Tongue still dry Everywhere marked capillary stasis Pulse 30 to the quarter small volume and rather running Heart sounds clear, first much like the second Abdomen is not distended Everywhere some rigidity No pain"

October 5 Patient still delirious, muttering and talking continually Marked subsultus tendinum Rigidity of the neck, and head is held somewhat retracted All the extremities are stiff and rigid, and there is a doubtful Kernig's sign Again the note is made that the first heart sound is of the same quality as the second The pulse still 30 to the quarter small and running

October 6 Patient's general condition not improved Marked gallop rhythm at the apex and reduplication of the second sound at the base

October 7 Still marked rigidity of the neck An occasional drop in the pulse rate

October 9 The following note by Dr McCrea "Patient's general condition much improved Active delirium still, although not as marked Pulse stronger and of better volume Blood-pressure has risen 20 mm of mercury since yesterday afternoon Rigidity of the neck and extremities not so marked Abdomen not held so rigid Slight degree of tympanites No tenderness"

October 13 Swelling noted under both submaxillary regions apparently involving the glands, and more marked on the left than on the right Swelling has come on with great rapidity The parotid glands are not involved

October 14 The following note was made 'Patient had a very uncomfortable night owing to salivation and difficulty in breathing The swelling of the

neck was decidedly more apparent at 11 than at 7 o'clock, especially on the left side, where it extended to the parotid region Redness and heat extended down over each clavicle Posterior cervical glands are decidedly larger A small abscess over the occiput was incised and about 10 c c of pus escaped The patient was delirious, requiring morphin Pulse fairly good Leukocytes at 8 30 a m were 16,000 Patient is decidedly easier this morning Swelling less marked The respirations are easier Cultures from abscess show *Staphylococcus pyogenes aureus*"

October 15, 1 30 a m There is the following note "Patient had been very restless during early part of the night, tossing about from side to side in the bed Breathing was less labored Swelling of the neck less pronounced Apparently there was slight fluctuation in the left submaxillary region, with a suggestion of pointing Discharge from the nostril continued as before Mind was totally impaired Although usually quiet, with eyes wide open, at times patient struggled to get out of bed Abdomen seemed natural At about 12 45 a hypodermic of morphin, grain ⅛, was administered Respirations became more rapid and shallow, but never labored and pulse suddenly fell A hypodermic of digitalin, gr 1/30, and strychnin, gr 1/30, was administered I was summoned, and on arrival, three minutes after, pulse was not perceptible at the wrist Heart impulse could not be felt at the apex There were a few spastic movements, no cyanosis, and patient was dead"

Clinical Diagnosis—Typhoid fever, cellulitis of the neck (angina Ludovici)

AUTOPSY

Pathological No 2192 Autopsy Oct 15, 1903 at 2 p m, by Dr MacCallum

Anatomical Diagnosis—Typhoid fever, swelling and ulceration of Peyer's patches and solitary nodules, acute splenic tumor, bronchopneumonia emphysema, atelectasis, arteriosclerosis of aorta and coronaries acute vegetative mitral endocarditis, phlegmonous inflammation of muscles of the base of the tongue

The body is that of a fairly well nourished man, 180 cm long The thorax is slightly deformed, the left side being prominent The neck laterally below the ears is markedly swollen Rigor mortis and livor mortis are well marked Over the back there are numerous furuncles The mucosæ are very pale Subcutaneous fat is small in amount The peritoneal cavity contains a clear fluid small in amount The surfaces are smooth The ileum, in its lower portion shows many dark areas which apparently correspond with ulcers Mesenteric lymph glands are much enlarged There are very much enlarged lymphoid glands in the omentum and retrosternal tissue

Thorax—Lungs are voluminous and meet in the middle line Pleural cavities are free from accumulation of fluid No adhesions over the lungs The pericardium contains about one liter of clear yellowish fluid Pulmonary arteries contain only fluid blood

Heart—Weight 320 gm The heart is not enlarged The surfaces are generally smooth Epicardium over the right heart is somewhat thickened and opaque There are a few minute hemorrhages The right auricle contains post mortem clot The tricuspid valve is normal The pulmonary valves are delicate The mitral orifice is about normal in size Along the line of closure of the anterior segment of the mitral valve there are numerous translucent vegetations The aortic valves are clear The heart muscle is rather soft opaque and gray There are scattered everywhere numerous more opaque distinct gray flecks or spots The anterior and descending branches of the coronary artery show numerous yellow flecks of sclerosis These are of small size from 1 to 2 mm in diameter Almost the whole of the intima is converted into irregular yellowish gray patches which

are not much elevated The walls of the smaller branches are also thickened The aorta shows only a very slight thickening, just above the valves In the wall of the left ventricle near the auriculoventricular ring there are a small number of patches in which the muscle is completely replaced by a grayish white, somewhat translucent fibrous tissue Two patches of this sort are found measuring 5 mm in diameter One or two minute hemorrhages are also found in the substance of the heart muscle

Lungs—The left lung is very voluminous and cushiony, except in the lower posterior portion of the lower lobe There the surface is shrunken and the lung substance is airless and of a deep purple color The bronchial glands are somewhat enlarged The bronchi contain frothy fluid The large arteries at the hilum of the lung are clear The branches flowing into the collapsed area show no alteration On section, the anterior portion of the lung is generally air containing, but there are scattered everywhere and especially through the lower lobe minute foci of consolidation with hemorrhages, arranged in small groups In the posterior portion there is also a number of such areas The atelectatic part of the lung is very superficial The right lung is also very voluminous It is everywhere cushiony There are over the base areas in which the pleural gloss is lost The large vessels are free from thrombi On cut section the upper lobe is found almost everywhere to be air-containing In the lower lobe foci of consolidation are thickly scattered as in the left lung Throughout the lungs the alveoli are very large

Spleen—Weight 300 gm., slightly adherent to the diaphragm and surrounding areas, has a brownish red color The capsule has a rough, dry appearance and is covered with fibrin There are numerous minute hemorrhages The consistency is greatly decreased On section the swollen splenic substance is extremely soft and pasty Numerous hemorrhages throughout The Malpighian bodies are enlarged and irregular

Neck Organs—The epiglottis and tissues about the larynx are edematous The left lobe of the thyroid is much larger than the right The trachea shows no abnormality In the tissue about the hyoid bone, especially on the left side, there are numerous small abscess-like foci scattered throughout the muscle, which feels firm and has a translucent appearance On removing the tongue from the mouth, it is found that in the neighborhood of the left sublingual salivary gland there is an abscess cavity about 1.5 cm in diameter, containing yellowish pus

Liver—The surface is smooth and rather grayish Small points of opacity show throughout the capsule On the surface the lobules are quite well marked out They have a gray periphery and dark red center There are no definite areas of necrosis to be seen The mucosa of the jejunum is normal in appearance The gall bladder is greatly distended The bile flows freely through the bile ducts

Pancreas and Adrenals—Normal

Kidneys—Cortical substance is opaque and swollen Numerous minute hemorrhages over the cortex Numerous hemorrhages in the mucosa of the pelvis which contains cloudy, bloody fluid

Intestines—Peyer's patches are swollen and have a pitted appearance with loss of substance Near the ileocecal valve the swelling is much more extensive, but there are no very deep ulcers and loss of substance is quite superficial In the cecum the solitary nodules appear superficially ulcerated

Aorta—The aorta shows beginning sclerosis about the intercostal arteries Along the aorta there are numerous large hemorrhagic lymph-glands There are small hemorrhages in the tissue

DESCRIPTION OF SECTIONS

The heart muscle shows very extensive parenchymatous and interstitial changes The fibers everywhere look granular The "cement lines" are rather prominent and in some places there is a little separation, but there is no marked fragmentation In some areas the striation of the cells is very indistinct and in others seems entirely absent Many of the muscle fibers show marked vacuolization on longitudinal section The nuclei are much swollen and vesicular Some of the nuclei are large empty bags, although in most, irregular strands of chromatin are preserved There is no marked pigmentation of the perinuclear spaces The spaces themselves are often greatly increased in size On cross section in some areas there is very extensive change in the appearance of the fibers The sarcoplasm is greatly increased in amount, the fibril bundles are diminished in size and number and, in some of the cells form only a circle about the periphery Throughout the various sections there are numerous areas of interstitial infiltration Many of these begin under the epicardium and dip down in between the muscle cells All of the connective tissue spaces throughout the heart are more richly cellular than is normal The cells in these areas consist mostly of small mononuclears with however many large mononuclears and some polymorphonuclears There are, too, numerous large cells with round or oval nuclei and of deep eosin staining protoplasm Some of these cells exhibit phagocytosis In several areas there is marked degeneration of the muscle fibers without any apparent interstitial infiltration In these areas the muscle bundles are filled with a granular material studded with muscle fibers which are diminished in size and have lost their characteristic striation In one place there is a large area where the muscle fibers seem to have disappeared completely There is marked periarteritis of one of the large branches of the coronary artery caught in the section

The papillary muscles are particularly the site of both parenchymatous and interstitial lesions Many of the smaller vessels show marked thickening of their walls, and in a few the lumen seems completely occluded by cells of the same character as those which have infiltrated the muscle There is in places marked edema of the connective tissue between the muscle fibers About some of the areas of infiltration there seems to be a formation of fresh connective tissue

SECOND CASE

Series No 15 Medical No 15015 Male physician, aged 25 Admitted to the hospital on Nov 8, 1902, died Nov 25, 1902 Clinical diagnosis typhoid fever, hemorrhage

History—The family history contains nothing of importance The patient had measles at the age of 21 mumps at the age of 23 and chicken pox at the age of 24, otherwise he was always strong and healthy

Present Illness—On November 2 the patient was taken with headache, general malaise, pain in the back and limbs These symptoms continued and on November 5 he had fulness of the neck with marked pain On the 6th he had hot and cold flushes lost his appetite and on the 7th developed nausea Bowels were constipated Temperature had ranged from 101 to 102 the two days preceding admission to the hospital

Examination—On the morning after admission—November 9—Dr McCrea made the following note Patient is well nourished and robust Sensorium clear Tongue very lightly coated gums and mucous membranes good color Thorax large and well developed Expansion good and equal Percussion note clear throughout Breath sounds everywhere clear Heart point of maximum impulse neither visible nor palpable Apex by stethoscope in the fifth interspace

7 75 cm to left of the midsternal line Area of dulness is not increased Heart-sounds clear throughout Pulse 24 to the quarter, full and good volume, dicrotic Abdomen is natural Respiratory movements well marked No definite rose spots, although there are a few suggestive ones No especial tenderness Some gurgling in the right iliac fossa Liver dulness in the right mammary line begins at the sixth rib and extends about 4 cm Spleen is not felt"

Course of Disease—After admission, patient's temperature was very high and he showed no response to the tubs There was considerable nausea and some vomiting Pulse remained good

November 13 It is noted that patient is very stupid and dull Definite rose spots are present on the abdomen The pulse remains good in quality, but both the respiration and the pulse rate show variations from time to time

November 19 On this day, following a sudden drop in the temperature, a little blood appeared in the stools The amount, however, was too small to have caused the sudden drop The following note was made by Dr McCrea "The patient is dull and drowsy Tongue somewhat dry and tremulous Thorax is clear on auscultation and percussion No abdominal features No distention or tenderness, and the respiratory movements are well marked When seen at 11 p m, the general condition was not so good The pulse was more rapid and of poorer quality" Later in the day this note was made 'Since last night the patient's general condition has not been so good He is more delirious and looks worse Pulse rate has been irregular and volume poorer Tongue is dry and tremulous At times a low muttering delirium No subsultus Respirations are rapid and vary much in rate Lungs are clear throughout on percussion and auscultation Heart sounds are clear The pulse rate varies from 128 to 150 Slight change in tension The abdomen is flat Respiratory movements well marked No tenderness, rigidity or muscle spasm" At 11 p m it is noted that the pulse is 108 to 112 and of decidedly better volume

Patient's condition the following morning was somewhat improved, but in the afternoon he again became worse and developed some hiccough At 11 p m the following note was made by Dr Osler 'Marked stupor and hebetude Respirations at times almost normal Pulse 120, varying both in force and rhythm Abdomen is soft Respiratory movements present No tenderness on palpation"

The following day the patient had considerable hiccough and occasional vomiting Pulse was slower and of better volume An enema brought away some changed blood

November 24 At 4 p m the following note was made "Patient had a sinking attack at 2 20 p m Pulse became very rapid 150 and was weak There was marked cyanosis Respirations 13 to the quarter Patient did not respond to questions Was stimulated heavily and received a one liter infusion of salt solution Rallied somewhat Maximum blood-pressure 78 mm of mercury Pulse rate 144 Ears very cyanotic" At 10 p m the patient's condition was described as very grave It is noted that the heart sounds are rather better than the pulse The attack of the afternoon is characterized in the notes as an acute cardiac break-down From this attack the patient never completely rallied

November 25 At 1 a m there is this note 'The patient is decidedly worse Quite unconscious Respirations over 60 Pulse cannot be felt at the wrist Heart sounds are not heard owing to the rapid noisy respirations After this the patient gradually sank and died at 2 10 a m

AUTOPSY

Pathological No 2033 Autopsy Nov 25 1902 at 8 30 a m, by Dr McCallum

Anatomical Diagnosis—Typhoid fever deep ulceration in small intestine limited ulceration in the colon acute splenic tumor general enlargement of the

mesenteric lymph glands cloudy swelling of the liver and kidneys, bronchopneumonia, beginning arteriosclerosis myocardial degeneration, occlusion of pulmonary arteries by cell masses

Abstract of Autopsy Notes—Body of a fairly well built man, 178 cm in length, moderately emaciated No edema Slight liver mortis Rigor mortis well marked Abdomen not distended Muscles very red Peritoneum dry Mesenteric glands greatly enlarged, dark purplish in color, the tissue overlying them deeply injected Considerable injection of the peritoneum throughout especially over the colon and small, red patches of subperitoneal hemorrhage Intestines nowhere greatly distended

Thorax—Lungs are quite voluminous but do not meet in the mid line Pleural cavity is free from adhesions and from excessive fluid Pericardium contains no excess of fluid

Heart—Weight 250 gm , is everywhere smooth Right ventricle is rather soft and flabby Over the surface of the right ventricle is a tendinous patch rather poorly outlined Left ventricle is quite firm and mottled in places Tricuspid and pulmonary valves are delicate The auricular appendage contains soft clots The left auricle also contains a soft clot The mitral valve is delicate The heart muscle on the left side is opaque, grayish in color, soft, the least touch on cut surface leaving a permanent impression The heart muscle shows some points and lines of yellowish opacity but on the whole is rather grayish pink and opaque The aortic valves are delicate There is beginning arteriosclerosis at the root of the aorta and there are one or two patches on the ventricular surface of the mitral valve There are numerous patches of yellowish sclerosis along the coronaries especially the anterior descending branch The posterior branch also shows extensive sclerosis The patches are small and discrete and in large part translucent, flecked with yellow Tangential sections of the heart muscles show everywhere the same dull opacity with only indefinite flecks of more yellowish color

Lungs—Voluminous injected and of a deep red color Several infarcts throughout the right lung and one particularly large one in the upper portion of the left lower lobe

Spleen—Tense rather soft and flabby and contains a few small hemorrhages under the capsule On section the Malpighian follicles are large and irregular The pulp is red and greatly swollen

Liver—Pale and rather pasty A few small hemorrhages over the left lobe On section the lobules are well defined with yellowish centers and more red peripheries The whole liver has a yellowish tint

Gall Bladder—Distended with dark green bile The bile duct is patent

Stomach—Numerous small erosions on the lower curvature The mucosa rather hyperemic

Intestines—Solitary follicles in the colon are visible, but not greatly swollen The upper portion of the colon very hyperemic and as far as the cecum there are several small quite deep ulcers Above the ileocecal valve there are four or five large deep ragged ulcers with slough adhering to the exposed musculature Above this for some distance all of Peyer's patches are involved many of them swollen with beginning slough in others the ulcers extend deep into the muscle Higher up swelling is the main feature There is general hyperemia of the small intestine

Pancreas—Normal

Kidneys—On section the whole kidney is rather pale, cortex somewhat swollen Striations regular and straight Glomeruli prominent Labyrinthine portion is swollen and somewhat opaque Pyramids are pale

Aorta—Shows delicate patches of sclerosis throughout its whole course These are narrow, stringy patches in which the yellow opacity is centrally placed

DESCRIPTION OF SECTIONS

The marked granular and fatty degeneration of the fibers which the gross description of the heart indicates are not apparent in the sections The fibers have a granular appearance and the striation is in places obscured The "cement lines" are prominent and there is some fragmentation The nuclei are swollen and the perinuclear spaces enlarged with some pigmentation at the poles The sarcoplasm is somewhat increased in amount and on cross section the fibril bundles are rather widely separated, but the change is not marked All of the blood-vessels contain more leukocytes than normal, and there is a diffuse scattering of cells throughout the interstitial spaces but no localized intense areas of infiltration A branch of the coronary shows well-marked endarteritis There is no noteworthy change in the small arteries

These two cases, although so similar in their clinical course, present anatomically widely different conditions In the first the parenchymatous and interstitial lesions are more marked than in any other heart in our series, and the acute inflammatory changes in the coronaries equally striking In the second, while the cardiac muscle is soft and opaque with lines of yellowish opacity, the microscopical examination of the fixed tissue shows surprisingly few fiber and no extensive interstitial lesions The fixing, of course, has obscured the granular and fatty degeneration, which must have been marked Sections from three different portions of the left ventricle were studied, so the investigation is not as complete as we would wish it to be The changes in the coronary arteries are extensive

Of the forty-one cases the cause of death may be roughly stated to be due to

	Cases
Perforation with subsequent peritonitis	10
Cholecystitis and peritonitis	2
Terminal pneumonia	2
Intestinal hemorrhage	2
Hemorrhage from mucous membranes of respiratory and digestive tracts (hemorrhagic typhoid)	1
Severe bloody vomiting	1
General staphylococcus septicemia and abscesses	2
Following convulsions	2
Toxemia	14
Sudden collapse	5

The term toxemia is an indefinite one but is used for want of a better It is applied to those cases in which death occured from the disease without the intervention of any direct complication The classi-

fication comprises then two groups of cases first, those in which death occurred, if not as the direct result of, at least concomitantly with, the development of serious complications twenty-two in number, and second, those in which death occurred directly as the result of the typhoid infection, nineteen in number

Of the 22 cases in the first group
0 showed marked circulatory symptoms
7 showed some circulatory symptoms
15 showed no circulatory symptoms
Of the 19 cases in the second group
11 showed marked circulatory symptoms
5 showed some circulatory symptoms
3 showed no circulatory symptoms

These figures are certainly an indication of the relative importance of circulatory disturbances in the causation of death in uncomplicated cases In the second group are five cases of patients who died rather suddenly and in whom to all appearances death was due to a sudden failure of the heart

THE RELATION BETWEEN THE CIRCULATORY SYMPTOMS AND THE MYOCARDIAL CHANGES

Of 12 cases in which there were well marked interstitial and parenchymatous lesions
In 5 there were definite circulatory symptoms
In 2 there were less marked circulatory symptoms
In 5 there were no definite circulatory symptoms
Of 3 cases in which there were well marked interstitial but only moderate parenchymatous lesions
In 1 there were definite circulatory symptoms
In 1 there were less marked circulatory symptoms
In 1 there were no definite circulatory symptoms
Of 12 cases in which there were moderate interstitial but well marked parenchymatous lesions
In 2 there were definite circulatory symptoms
In 7 there were less marked circulatory symptoms
In 3 there were no definite circulatory symptoms
Of 2 cases in which there were only moderate interstitial and parenchymatous lesions
In 1 there were minor circulatory symptoms
In 1 there were no definite circulatory symptoms
Of 7 cases in which there were no definite interstitial but well marked parenchymatous lesions
In 3 there were definite circulatory symptoms
In 4 there were no definite circulatory symptoms
Of 5 cases in which there were no definite interstitial and only moderate parenchymatous lesions
In 1 there were minor circulatory symptoms
In 4 there were no definite circulatory symptoms

While patients with even marked interstitial and fiber lesions frequently show during life no prominent circulatory disturbances, it is rare not to find well-marked anatomical changes when such disturbances are present While the correspondence between the myocardial changes and the clinical picture are by no means constant, the foregoing summary indicates a close relation Such variations as occur are well known clinically The sudden and unexpected deaths during convalescence after a mild and uneventful diphtheria are illustrations When occasionally the grave lesions anticipated from the symptoms during life are missed, it can only be assumed that the histological picture may not always faithfully express the extent of injury the fibers have sustained I must also again remark that in some of my cases the area of heart muscle studied was too small to allow of anything like a satisfactory conclusion about the condition of the organ as a whole What I mean by "circulatory symptoms" I have previously explained They are symptoms which in all likelihood arise *from* some damage *to* the heart itself and are not the usual circulatory derangements consequent to vasomotor paralysis As has been previously noted, five patients died apparently of cardiac failure All showed definite myocardial lesions and in four the changes were well marked

One would presume that cardiac lesions would be more common in patients dying of the typhoid infection itself than in those dying after fatal complications, notably after perforation of the intestine or the gall-bladder

Of the 19 patients dying of "toxemia"
7 had marked interstitial and parenchymatous lesions
1 had marked interstitial and moderate parenchymatous lesions
6 had moderate interstitial and marked parenchymatous lesions
4 had no interstitial but marked parenchymatous lesions
1 had only slight parenchymatous lesions
Of 12 patients dying from peritonitis (10 after perforation of intestines 2 after perforation of gall bladder)
0 had marked interstitial and parenchymatous lesions
1 had marked interstitial but moderate parenchymatous lesions
4 had moderate interstitial and marked parenchymatous lesions
1 had marked interstitial and moderate parenchymatous lesions
2 had no interstitial but marked parenchymatous lesions
4 had no interstitial and only slight parenchymatous lesions

Of sixteen cases in which there was irregularity of the pulse in all but two there were marked parenchymatous lesions and in only three were interstitial lesions entirely absent

Of the eight cases in which there was a systolic murmur at the apex in 4 there were extensive interstitial and parenchymatous lesions in 4 definite parenchymatous but no interstitial changes

THE SIGNIFICANCE OF THE HEART MUSCLE CHANGES IN TYPHOID FEVER

In spite of the extent to which the heart muscle is damaged in typhoid fever it is a difficult matter to determine how far the functional capacity of the heart is impaired Stokes called attention to the frequent lack of correspondence between the severity of the disease or the prominence of circulatory symptoms and the degree of anatomical change in the heart muscle The most marked lesions are sometimes found when one would least expect them and the lesions are sometimes mild when the clinical course of the disease would lead us to predict their presence In the section where I have compared the clinical symptoms of the disease and the histological picture of the heart muscle the lack of any constant relation is apparent It may be that the muscle cells are often more severely injured than one would judge from the structural changes they present and it is indeed remarkable what a high grade of efficiency the heart may preserve in spite of the existence of very extensive fiber lesions I have however noted that where the circulatory symptoms have been unusually prominent and particularly where death has seemed due to sudden cardiac failure, extensive myocardial lesions have almost constantly been present On the other hand, in some cases in which there were no unusual circulatory symptoms during life, quite as extensive myocardial lesions have been found Krehl[25] has suggested that the character of the toxin and the position of the lesions may be matters of primary importance Albrecht-[26] has particularly emphasized the significance of the position of the lesion From his anatomical studies he has attributed great importance to special bands of muscle fibers in the proper coordination of the heart-beat and believes that lesions involving certain areas would produce far greater damage than the same lesion situated elsewhere Aschoff and Tawara[19] refuse to accept the anatomical conclusions of Albrecht and reject the pathological assumptions based on them They in turn are particularly interested in lesions which may interfere with the impulse-conducting fibers of the bundle of His Tawara has previously published an excellent anatomical study of the distribution of this bundle The effect that lesions in various branches of the bundle may have on the rhythm of the cardiac movements and what effect if any they may exercise on the functional capacity of the heart are questions to be solved The ramifications of His bundle are particularly rich just under the endocardium and as areas of cellular infiltration are especially common there Aschoff and Tawara

25 Krehl Erkrankungen des Herzmuskels p 107
26 Albrecht Der Herzmuskel Berlin 1903

suggest the association as a possible explanation of the irregularities common in infectious diseases

It is a much-discussed question how far granular and fatty degeneration impairs the functional capacity of the heart Clinically in conditions where they are most extensive, as in phosphorus poisoning and anemia, we miss serious circulatory symptoms Experimentally the lack of relation between the two is even more striking [27] It is remarkable, too, how large an area of the heart muscle may undergo necrosis without appreciably impairing its function [25]

Nothing more definite can be said about the significance of fragmentation There are certainly no characteristic symptoms associated with the lesion as Renaut and Landouzy [28] at first thought Von Recklinghausen, in 1890, contended that the tears occur as the result of perverse contraction at the moment of death This view, that the occurrence of the lesion is an agonal event, has been generally accepted It is assumed that certain areas of heart muscle die a little before others and the contractions of the still living fibers tear them asunder Still the exact mechanism by which they are torn into so many fragments does not appear clear The lesion is such a common one and occurs in so many different conditions that no pathological importance can be attached to it

Changes in the fibrillar structure of the muscle must certainly interfere with the functional activity of the cell but these lesions we have not found extensive enough to assume that so large a number of fibers were affected as to compromise the efficiency of the heart as a whole Vacuolization and changes in the distribution of the sarcoplasm are lesions no doubt of still graver importance for the life of the cell, but these are no more frequent than the fibrillar lesions

The changes in the nuclei have given rise to some discussion Weigert [29] thought the large vesicular forms represent the first stage in division and multiplication and this view has been supported by Oertel [30] The publications of Ehrlich,[31] Romberg and Krehl leave little doubt, however, that they are distinctive marks of degeneration Krehl [32] has found changes in the size and shape of the perinuclear spindle of sarco-

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27 Lubarsch and Ostertag Ergebn d allgem Path u path Anat 1903 ix 612

28 Quoted by Lubarsch and Ostertag Ergebn d allgem Path u Path Anat 1903 ix 612

29 Weigert Samml klin Vortr (Volkmann's), 1878 162 163 quoted by Albrecht Der Herzmuskel p 245

30 Oertel Quoted by Albrecht Der Herzmuskel p 245

31 Ehrlich Charité Ann 1878 v 198

32 Krehl Erkrankungen der Herzmuskel p 165

plasm more constantly associated with cardiac insufficiency than any other single lesion He ascribes great importance to its presence Aschoff and Tawara are skeptical of the significance of the various fiber lesions described The nuclear lesions and the increase in sarcoplasm, especially they believe, are often more apparent than real

As the nuclei and sarcoplasm represent the essential living structure of the cell, changes in these are of primary importance as concerns its life A fiber may probably recover and be restored to activity even when granular and fatty degeneration and fibrillar lesions are extensive Albrecht[26] believes that restitution is possible even when the nuclei show marked vesiculation When a cell, however, has once died, it is improbable that its place can be filled by newly formed fibers There is no conclusive evidence of regeneration of cardiac fibers

From the careful observation of Mollard and Regaud it seems probable that interstitial lesions occur much later than the fiber lesions and that they are seldom present earlier than the end of the second week As circulatory symptoms when they occur tend to appear during the third week, the inference is near that they have an important bearing on their development The exact manner in which these areas of interstitial infiltration affect the functional activity of the heart does not seem clear, but the clinical evidence of their significance is indisputable"[7]

Every death during an uncomplicated acute infectious disease is a circulatory death and in every circulatory failure two factors are of importance the propelling force and the peripheral resistance or the heart and the vasomotor system What part does the heart and what part does the vasomotor system play in the deaths from acute infections and in the development of the symptoms frequently observed during the course of the disease and during convalescence?

Certain of these symptoms are unquestionably due to alteration in the heart itself The not infrequent dilatation with relative mitral insufficiency the cardiac irregularities and the changes in rhythm notably endocardial can have no other origin The unusually rapid or unusually slow pulse in all probability depends upon myocardial lesions It is during convalescence that symptoms of cardiac insufficiency make their appearance most clearly Prolonged irregularity of the pulse unusually rapid heart action breathlessness and fatigue on exertion a persisting mitral insufficiency occur frequently enough to indicate the extent and importance of the changes the heart muscle has undergone The tragic sudden death so common during convalescence from scarlet fever and especially from diphtheria is unusual after typhoid and the

[7] See particularly Romberg Deutsch Arch f klin Med 1891 xlvii 369

greater severity of circulatory derangements in the two former diseases stands in direct relation to the more common and more extensive myocardial lesions that obtain Still an occasional sudden death and more commonly prolonged invalidism after typhoid attest the importance of the cardiac changes in this disease [34]

It is difficult to determine the relative importance of the fiber and the interstitial lesions in the development of these symptoms If Renaut is right in contending that the interstitial changes are but secondary to the fiber damage and their extent dependent on the severity of the parenchymatous lesion, the question has no significance Those unwilling to accept this position will see in the time of occurrence of the symptoms, towards the end of the disease and notably during convalescence, and in the almost constant association of intense interstitial lesions with severe cardiac manifestations, an important indication This relation is particularly striking in the sudden deaths after diphtheria Circulatory symptoms are especially common and grave in diphtheria infections and it is in this disease that the interstitial lesions are most extensive and most striking

During the height of an infectious disease it is more difficult to determine the relative importance of myocardial lesions and of vasomotor paralysis in the circulatory failure Here, too, it is probable that sudden and unexpected death is due to cardiac failure and in some cases the symptoms of cardiac disturbance are so striking that we cannot hesitate to ascribe the essential part of the circulatory failure to the myocardial lesions In the more common types of the disease vasomotor paralysis would seem to be the essential factor Romberg, Passler and Binns,[35] from an admirable experimental study conclude that even when the myocardium is the seat of an extensive lesion it may remain perfectly efficient during the height of the infection death being then due entirely to vasomotor paralysis Their methods of investigation cannot be briefly presented nor can the criticisms of von Stejskal, who attempts to discredit their results Von Stejskal,[36] working in von Bach's laboratory, measured the auricular and the arterial pressures and in their variation

34 Excellent clinical pictures in Krehl (Erkrankungen des Herzmuskels p 280) Romberg (Deutsch Arch f klin Med 1891 xlviii 369 also Krankheiten des Herzens Stuttgart 1906 p 328) and Leyden (Ztschr f klin Med 1882, iv 334)

35 Romberg Passler und Binns Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstorungen bei acuter Infectionskrankheiten Deutsch Arch f klin Med 1899 lxv 652

36 Stejskal Kritisch experimentelle Untersuchungen über den Herztod im Folge von Diphtheretoxin Ztschr f klin Med 1902, xlvi 367

sees direct evidence of circulatory stasis and concludes that the heart must play at least an important rôle in the circulatory failure

Of the arterial changes in typhoid fever we have been able to make but a limited study A few cases exhibited endarteritis and periarteritis of the larger branches of the coronaries but the sections could not be used to determine the extent and frequency of the lesions The extensive changes in the smaller arteries noted by Hayem, and on which he lays so much importance, have been missed by other authors and they are certainly not present in my material Such arterial lesions as I have found might, however, exert some influence on the immediate outcome of the disease and particularly on the subsequent integrity of the circulatory system They are in most cases, hardly extensive enough to interfere seriously with the nutrition of the heart muscle but are important factors in the development of subsequent arteriosclerosis Thayer has shown that the average blood-pressure of individuals having had typhoid fever is higher than that of those who have escaped it and the radial arteries more frequently thickened We are coming to ascribe a more and more important rôle to the infectious diseases in the production of chronic arterial changes

The acute myocardial lesions are also significant for the subsequent well-being of the patient The destruction of muscle fibers and the large areas of interstitial infiltration leave scars which must influence the future efficiency of the heart Landouzy and Siredey report a case of death in a second attack of typhoid fever in which they found, besides acute myocardial lesions old fibrous scars which they ascribe to the first attack, there being no evidence of arterial disease One of Romberg's scarlet fever subjects showed cardiac scars which Romberg considers the remains of a previous attack of typhoid fever Mollard and Regand have found fibrous areas in the hearts of their dogs killed a year after treatment with diphtheria toxin

SUMMARY

The anatomical lesions produced by typhoid fever in the heart and blood-vessels have long been known While there is much diversity of opinion about the extent and frequency of the lesions their occurrence and importance is unquestioned In my study of forty-three hearts from patients dying of typhoid fever I was able to find some changes in practically all although in most the lesions were not extensive enough to allow one to assume with certainty that the efficiency of the heart mus-

was compromised There is unfortunately no satisfactory evidence at hand to allow one to judge the functional capacity of the heart by the character and extent of the histological lesions and frequently the two seem not to run parallel In at least six of my cases both the fiber and interstitial lesions are so intense that I could hardly associate their presence with complete efficiency of the organ I do not find any evidence of wide-spread change in the smaller branches of the coronary arteries but frequently periarteritis and endarteritis in the large and medium-sized branches No doubt these lesions must in some degree interfere with the nutrition of the heart and are of importance both for the immediate efficiency of the organ and its future integrity

There are certain symptoms during the course of an acute infectious disease which point directly to the presence of some cardiac lesion and often to cardiac insufficiency, notably irregularities of rhythm and the physical signs of beginning dilation Certain sudden deaths can be satisfactorily explained only upon the assumption of abrupt cardiac failure Romberg has asserted that during the height of an infection the circulatory failure depends entirely on vasomotor paralysis Even though the vasomotor system plays the important rôle, the work of Stejskal shows that the heart is not always perfectly efficient and that it cannot be entirely disregarded as a factor in the failure It is during convalescence particularly that the symptoms of a damaged myocardium stand out most clearly Such symptoms are not nearly so common after typhoid as after other infections, notably diphtheria, but they occur frequently enough to indicate the significance of the damage the heart has sustained

Undoubtedly these lesions of the myocardium and of the arteries are of the greatest importance for the future health of the individual We are being more and more deeply impressed with the significance of infectious disease in the production of chronic arterial and myocardial disease Typhoid fever has not in this regard the same importance as rheumatism, syphilis, or diphtheria but on account of its prevalence is a factor to be seriously reckoned with The prevention of infectious diseases will probably prove one of the strongest prophylactic measures against the degenerative lesions of the circulatory system

21 West Franklin Street

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

Pathological No	Age	Sex	Color	Duration of Illness	Cause of Death	Main Clinical Features
2440	10	F	B	18 days	Toxemia	Onset abrupt with vomiting and dizziness and marked mental features Admitted on 7th day of disease Was deeply intoxicated and had symptoms of meningeal irritation High fever Pulse rapid and irregular Apical systolic murmur developed while child was in hospital
2390	49	M	W	60 days	Peritonitis following intestinal perforation and operation	Onset indefinite Had been ill 3 weeks before admission with pain in hip and loss of appetite and general malaise No special symptoms until 42nd day, when he had a hemorrhage of about 15 c c Following this became very dull and deeply intoxicated On 46th day signs of perforation Operation After operation patient remained very stupid and toxic On 55th day signs of peritoneal irritation reappeared but patient's condition did not permit of a second operation No definite circulatory or cardiac symptoms except well marked arteriosclerosis Heart sounds described as somewhat muffled
2385	22	M	W	35 days	*Staphylococcus aureus* septicemia	Onset with headache and general malaise 4 days before admission Was irrational and deeply intoxicated on admission A severe infection Hemorrhage of 100 to 300 c c on 20th and 21st days On 17th day abscess in thigh opened followed by a profuse crop of boils Severe hemorrhage on the 24th day *Staphylococcus aureus* cultivated from the blood No special circulatory symptoms
2376	22	M	B	28 days	Peritonitis following intestinal perforation and operation	Onset with chill fever and headache Admitted on 6th day Dull but in good condition Later patient became irrational and delirious On 24th day symptoms of perforation and of pneumonia On 25th day operation on a moribund patient No circulatory symptoms
2373	33	M	W	46 days	Peritonitis following perforation	After an indefinite illness of 5 weeks the last two having been spent in bed patient entered hospital Was very ill on admission and soon became deeply intoxicated The last five days of life his condition was desperate and on the last two days had a number of small hemorrhages Perforation was not diagnosed and was probably a terminal event On admission pulse a little irregular and at end of disease was markedly so The first sound at apex was dull and muffled
2252		F				History lost
2199	15	M	B	22 days	Cholecystitis with localized peritonitis Pneumonia meningitis	Entered hospital after an illness of 15 days consisting of fever chills headache and languor Was dull and emaciated on admission Symptoms throughout were those of meningeal irritation Patient died in coma on 22nd day of disease Last few days of life had much abdominal pain and tenderness Pulse showed marked variations in quality and in rate
2197	43	M	W	65 days	After a prolonged illness died suddenly after being turned over in bed	After a 5 weeks illness with chills and fever and diarrhea during which time he had worked almost continuously he entered hospital During the month patient was in hospital never had a high fever but there was marked prostration Diarrhea was a prominent symptom The pulse from admission on was rapid weak and irregular For several days when temperature was subnormal it remained over 90 Became very weak and died suddenly after being turned over in bed Abundant albumin in urine
2192					Cited in the text	
2184	20	M	B	22 days	Intestinal hemorrhage	Entered hospital after weeks illness Was dull stuporous and deeply intoxicated on admission Pulse [illegible] Died from severe intestinal hemorrhage and died the [illegible] day

omical Diagnosis	Description of Heart — Gross	Description of Heart — Microscopical
with hyperplasia and ulcero-phoid follicles of small and nes Acute splenic tumor le infarcts Cloudy swelling Marked lymphadenitis of lymph glands with necrosis of gall bladder Pseudo lobar Acute fibrinous pleurisy	Somewhat enlarged weight 200 gm Peri cardium opaque and somewhat thickened, especially along the vessels Valves nor mal Muscle of left ventricle rather pale and cloudy-looking	The fibers look granular and in some places there is segmentation The nuclear changes are well marked No interstitial lesions except in one place under the epi cardium there are many large round cells
with ulceration of the ileum General fibrinopurulent peri-cute splenic tumor Cloudy liver and kidneys Chronic tricuspid endocarditis Slight osis Chronic adhesive pleu t side Compensatory emphy-ght lung Healed tubercul ous right lung	Weight 230 gm Tricuspid and mitral valves show slight thickening along bor-ders Muscle rather soft and brownish-red in color Cloudy on tangential section	Fibers look granular On cross section there is seen an increase of sarcoplasm with contraction of fibril bundles Some seg-mentation and fragmentation The nuclear changes are marked and there is a striking increase in the amount of pig ment Marked chronic interstitial and vascular changes Some diffuse intestinal collections of cells
ver General septicopyemia bscesses in kidneys and right ucroma of aorta and coronary Bronchopneumonia Typhoid of the ileum and large intes	Rather small weight 200 gm Firm Muscle of a light brown color and a little pale Quite firm and not friable	Fibers look swollen and granular Markings are indistinct Nuclear changes are well marked and there is considerable pigment No special interstitial changes
er Perforation of cecal ulcer rulent peritonitis Bronchopneu Chronic fibrinous pleuritis Fatty lon of liver with chronic peri Cloudy swelling and congestion ys	About normal size weighing 220 gm Mus culature of left ventricle soft and flabby On tangential section decidedly cloudy Fresh sclerosis in aorta and coronaries	Fibers look granular Nuclear changes fair ly well marked and some pigmentation Some sections show considerable segmenta tion No special interstitial changes Section of coronary artery shows patch of fresh sclerosis
ceration with extensive ulceration olon Hemorrhage Perforation itonitis Bilateral hydrothorax monia Chronic passive con of lungs and viscera Acute tumor Cloudy swelling of liver neys	Somewhat increased in size weight 380 gm Pericardium smooth and glistening Mus culature of left ventricle considerably hypertrophied Is firm and of good color but on section appears markedly cloudy Fresh sclerosis of aorta and coronaries	Fibers appear granular and on cross section some increase in sarcoplasm Nuclear changes are well marked and there is moderate pigmentation Some segmenta tion Definite areas of cells under epi-cardium which in places dip down between the muscle fibers The cells are mostly small mononuclear with some polymorpho nuclears and many large endothelioid cells
ver Operation (amputation of Infected abdominal wound and atelectasis of lungs Broncho nia Cloudy swelling of liver and Edema and swelling of pancreas e abscesses of kidneys Acute tumor Early arteriosclerosis g ulcers in small intestines	About normal in size Muscle pale anemic and rather cloudy The tissue has a yel lowish color especially marked in the papillary muscle	Fibers are rather granular Some increase of sarcoplasm Nuclear changes well marked Moderate fragmentation No special interstitial lesions
fever Swelling and ulceration of patches and solitary nodules ropneumonia Acute cholecystitis ulceration and localized peritonitis cerebrospinal meningitis	Slightly larger than normal Muscle rather flabby and slightly mottled in appearance but not markedly opaque Fresh sclerosis of aorta and coronary	Fibers a little granular Nuclear changes not marked One section shows slight fragmentation No definite interstitial changes
fever Ulceration of ileum and Marked consolidation of lungs gangrene Cirrhosis of the liver ic diffuse nephritis	Not enlarged Sclerotic patches on back of anterior mitral leaflet and at root of aorta Muscle is grayish pink in color and rather soft On tangential section somewhat mottled and opaque	Some fibers look granular Moderate frag mentation Nuclear changes well marked but not extensive Considerable pigmenta tion Many areas of accumulation of small round cells under epicardium but no invasion Throughout the connective tissue spaces the cells are unusually numerous but no areas of marked infiltra tion Some of the artery walls show a chronic thickening
d fever Hyperplasia and ulceration lymphatic structures of small and intestines Hemorrhage into bowel a cecal ulcer Cloudy swelling of Acute nephritis Acute splenic or	Weight 280 gm Normal in size Muscle pale and somewhat soft Slight sclerosis at base of aorta	Fibers look granular In some the longi tudinal striation is obscured Some vacuolization On cross section some in crease of sarcoplasm Marked nuclear changes with pigmentation Marked seg mentation Capillaries unusually full of leukocytes Several areas of consid rable interstitial infiltration Many large and small round cells and a few eosinophils

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

	Age	Sex	Color	Duration of Illness	Cause of Death	Main Clinical Features
8	31	M	W	16 days	Toxemia	Was so ill on admission to hospital could give no history Sister says he had been ill for a little over 2 weeks with fever, diarrhea and blood in stools On admission he was stupid, sallow and emaciated Pulse was rapid and irregular and there was a loud systolic murmur at apex with some accentuation of pulmonary second sound
91	31	M	B	18 days	Toxemia	Onset 2 weeks before admission with headache and fever Was very ill on admission dull and irrational Became extremely intoxicated and died 4 days later Pulse was small and fast Heart sounds muffled Pulmonic second sound accentuated Marked gallop rhythm for 4 days before death
66	17	M	W	17 days	Peritonitis following intestinal perforation	Taken ill 10 days before admission with headache chill and fever On admission was very ill and dull *Became actively* delirious and on the 7th day had perforation followed by operation and death No circulatory symptoms except a soft systolic murmur at apex and over body of heart
952	32	M,	W	3 months	Exhaustion Death came rather suddenly	A most unusual clinical course Entered hospital after 1 weeks illness with headache malaise and fever On the 27th hospital day temperature reached normal only to start off again on an intermittent relapse During this relapse the patient's condition was worse than during the original illness He looked ragged and fever eaten After 2 months of fever the temperature reached normal Remained normal for 15 days during which patient improved then started up again, and patient died, wasted and worn 48 days later The only notable circulatory symptom was an unusually rapid pulse During the intercurrent relapse he had several sinking spells In one the pulse going to 160 At this time, too, heart sounds had a tendency toward embryocardia At the end death came suddenly
1029	28	F	B	3 months	Cited in the text Exhaustion toxemia	Entered hospital after having been ill for 3 weeks with *chills fever, nausea and vomiting* Was extremely ill on admission and it seemed probable that she would die at any time On 31st day in hospital had a sudden drop in temperature followed by four chills in the next few days On the 9th day pneumonia developed On the 41st day developed a cellulitis back of left ear From 43rd day on fed almost entirely by stomach tube Toward the end there was marked abdominal distention due to acute dilatation of the stomach Anemia was a prominent feature on *admission and throughout the illness* The pulse was unusually rapid and at times a little irregular Heart sounds are described on one occasion as approaching embryocardia, on another that the first sound is reduplicated
1041	21	M	B	32 days	Toxemia	Entered hospital on 9th day of illness Was deeply intoxicated and very ill on admission Became delirious and then very dull For 2 days before death was lethargic Considerable albumin in urine No special cardiac or circulatory symptoms Pulse described once as being a little irregular in force Soft systolic murmur over body of heart
1045	5	M	W	7 weeks	Toxemia	Ill for 6 weeks before entering hospital On admission was desperately ill with marked meningeal symptoms Typhoid bacilli obtained from spinal fluid although there was no meningitis at autopsy Pulse was very rapid and weak Embryocardia No murmurs Died 6 days after admission to hospital the meningeal symptoms persisting to the end
1067	29	M	W	26 days	Peritonitis following perforation	Was taken acutely ill 3 weeks *before admission with fever* and general malaise Was in good condition on admission After 9 days in hospital had several hemorrhages amounting in all to about 1 liter On the 11th day perforation followed by operation Stood operation well but following day developed bilecough and died on the 14th day No special circulatory symptoms
1080	17	M	W	22 days	Cardiac failure	A very severe attack of typhoid fever admitted on 11th day of illness In a very grave condition and during whole time in hospital was *desperately ill* Was filthy, irritable and delirious and finally stuporous Death followed by collapse hours after a collapse apparently due to cardiac failure On admission it was noted that first and second sounds were alike in quality and later the second sounds Pulse was irregular for 4 days before death

Anatomical Diagnosis	Description of Heart — Microscopical	Description of Heart — Gross
fever Swelling and ulceration of s patches and solitary follicles Retroneal hemorrhage Cloudy swell of heart, liver and kidneys Acute le tumor, swelling of mesenteric glands Arteriosclerosis	Muscle of medium firmness Pale red color On tangential section shows a number of small yellowish spots and a few minute hemorrhages Papillary muscles show some hemorrhages	Marked vacuolization of fibers, especially on cross section Some segmentation Nuclear changes are particularly marked and there is extensive pigmentation All the connective tissue spaces are richly cellular and there are numerous areas of considerable infiltration Both the fiber and interstitial lesions are quite well marked
l fever Ulceration of colon and of l intestine Cloudy swelling of liver idneys Bronchopneumonia Hemorie infarction and edema of lungs	Not enlarged Epicardium in places thickened and white Muscle of right ventricle flabby and soft Muscle of left ventricle rather gray and somewhat opaque but shows no distinct patches of fibrous tissue	Fibers show no marked changes Nuclei are large and vesicular but not extensively so Some increase of sarcoplasm No segmentation Some small round cells throughout the connective tissue strands but no large areas and no infiltration
dinal operation wound Typhoid fever ration of ileum and cecum and mucosa appendix Perforation of ulcer in u General peritonitis Abscess tion in both lungs Bronchopneuia, fibrinopurulent pleurisy	Not enlarged Fairly firm in consistency Muscle gray and rather soft Homogeneous in appearance No evidence of fatty change	Sections show very few changes Some nuclei are moderately swollen and the perinuclear space enlarged Some "cement lines" are visible Capillaries are rather full No interstitial infiltration
id fever Fresh and healing ulcers in colon Hyperplasia of the lymphds Acute splenic tumor Bronchoamonia Typhoid ulcers in the appdix Focal areas in the liver	Not enlarged Surface smooth Muscle somewhat soft On section not homogeneous but shows opaque yellow patches scattered here and there Root of aorta shows a few small patches of beginning sclerosis Several patches of fresh yellow sclerosis in coronaries	Very extensive nuclear changes Greatly swollen and perinuclear spaces much increased Some fibers show vacuolization On cross-section well-marked and wide spread increase in sarcoplasm Some segmentation Many small areas of cellular accumulation throughout the interstitial tissue and notably about the blood-vessels No infiltration from these areas Some chronic fibroid patches Arteries show some chronic thickening
oid fever Healed ulcers in the intes es Dilatation and displacement of omach Encapsulated fibrinopurulent urisy Bronchopneumonia Chronic olifferative pelvic peritonitis Fatty de neration of the myocardium	Weight 250 gm Superficially everywhere smooth Muscle rather grayish Soft and flabby, and fairly homogeneous On tangential section shows a uniform grayish opacity In papillary muscles some opaque yellowish specks and a close inspection of their endocardial surface shows the mottling characteristic of fatty degeneration	The nuclear changes are well marked The fibers look a little granular The perinuclear spindle is enlarged and there is moderate pigmentation Marked fragmentation Beneath the epicardium numerous collections of cells which dip down between the muscle bundles Small areas of cellular accumulation throughout the section Cells are mostly small mononuclears, but there are many polymorphonuclears and some large mononuclears
hoid fever Multiple ulcers in jejunum leum and large intestine In small intes ine ulcers are sloughing, in large ne nfiltment and diphtheritic Enlargement of retroperitoneal and mesenteric glands One suppurating gland Fatty degeneration of heart muscle Great emaciation Bed sore Acute bronchopneumonia	Weight 200 gm Normal size Muscle pale and yellowish brown in color Consistency soft	Fibers do not show the marked fatty degeneration described in gross specimen Look granular but striation well preserved Some fragmentation Nuclear changes marked Some fibers show vacuolization but this change not marked Some scattered cells throughout the interstitial tissue but no definite interstitial infiltration
phoid fever Swelling and ulceration of Peyer's patches with slough formation Hyperplasia of lymph glands and spleen Focal necroses of liver Bronchopneumonia	Weight 80 gm Pericardial layers edematous Heart extremely soft and flabby Muscle has a watery appearance grayish yellow in color The organ is excessively soft and collapses in the hand	In spite of the extreme softness of heart muscle the microscopic lesions are not especially striking Moderate nuclear changes with some pigmentation Considerable sarcoplasmic increase Slight fragmentation Collections of small round cells under epicardium and about blood vessels but no tendency to infiltration
yphoid fever Operation wound Suture of perforated intestine Diffuse peritonitis Emphysema of all organs (gas bacillus)	Weight 380 gm Epicardial surface smooth Coronary arteries filled with gas Muscle extremely soft and flabby Has a gray granular appearance on section	Fiber changes are definite but not striking *Extensive fragmentation some nuclear* change and a little pigmentation No marked increase in sarcoplasm Fibers appear granular Hemorrhage between fibers Collections of small and large round cells about blood vessels but no interstitial infiltration
Typhoid fever Sloughing ulcers in the Ileum and colon Distention of intestines Hyperplasia of mesenteric lymph glands Acute splenic tumor Lobar pneumonia Acute serofibrinous pleurisy	Weight 220 gm Surface smooth Muscle fairly firm and of a uniform brownish red color	Slight fragmentation Nuclear changes *moderate* Some sarcoplasmic increase About blood vessels and throughout interstitial bands small collections of small and large round cells No definite interstitial infiltration

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

Series No	Pathological No	Age	Sex	Color	Duration of Illness	Cause of Death	Main Clinical Features
21	1884	19	M	B	14 days	Peritonitis following perforation	Onset 5 days before admission to hospital with fever headache and stiff neck In good condition on admission but temperature was high On 6th day developed abdominal pain Abdominal symptoms became more marked and patient died on 9th hospital day
22	1827	42	M	W	36 days	Toxemia Hemorrhagic typhoid	Admitted after having been ill nearly 4 weeks with chills and fever and headache On admission was sallow and emaciated and very ill Developed numerous hemorrhages into skin and had blood in stool and sputum Became very dull and stupid and the last few days of life had marked dyspnea Heart sounds were faint and distant Pulse markedly irregular the last 10 days Radial arteries considerably thickened
23	1806	33	F	B	Indefinite	Died in coma after convulsions	Patient very ill when she entered hospital Shortly after admission had a number of severe convulsions passed into coma and died 7 hours after Clinically the case was considered to be uremia and a correct diagnosis was made only at autopsy The history given was that patient was taken suddenly ill with a sharp chill 5 days before admission No cardiac symptoms made out but the examination was not satisfactory
24	1786	38	F	W	22 days	Peritonitis following cholecystitis and perforation of gall bladder	Patient admitted to hospital dull and ill after 2 weeks of fever headache and diarrhea On admission had pain and tenderness in right hypochondrium Signs of peritonitis became more and more prominent No special circulatory features
25	1774	32	M	W	13 days	Toxemia	Taken ill 12 days before admission with fever and general constitutional symptoms On admission was irrational and stupid Pulse became rapidly weaker and the patient cyanotic and the following day died Patient was extremely obese No circulatory features
26	1768	14	M	W	9 days	Toxemia	Patient had previously been in the hospital with malaria and Addison's disease Was taken abruptly ill 2 days before admission with fever Was deeply intoxicated on admission and grew gradually worse and died on 6th hospital day No circulatory features
27	1634	26	M	W	14 days	Toxemia	Onset of illness 10 days before admission with fever headache and weakness Had been delirious before admission Was extremely ill when he entered hospital High fever and delirium Became more and more deeply intoxicated and developed a marked tremor Died on 4th hospital day On admission pulse was very irregular and remained so at intervals Heart sounds clear but approaching embryocardia
28	1642	22	F	B	Apparently 18 days	Toxemia Death preceded by bloody vomiting	Admitted to gynecologic service complaining of abdominal pain Operated on and tubes removed 22 days later a second operation for release of intestinal adhesions Thirteen days after second operation temperature began to rise 12 days later patient began to vomit blood and continued for 4 days when she died from exhaustion Throughout course had considerable abdominal pain No unusual circulatory symptoms

Anatomical Diagnosis	Description of Heart	
	Gross	
ld fever Hyperplasia of lymph nodes intestine with ulceration of Peyer's hes in the ileum and perforation eral fibrinopurulent peritonitis Acute nic tumor Hyperplasia of abdominal ph glands Bronchopneumonia and ulent bronchitis	Weight 220 gm Not enlarged Pericardial and endocardial surfaces smooth Muscle flecked with grayish points and somewhat opaque in appearance	I
ld fever Clean ulcers in lower ileum te splenic tumor Pyelitis and sup itive nephritis of right kidney Edema lungs Effusion into pleural cavities	Weight 300 gm Not enlarged Muscle fairly firm, deep red in color and homogeneous	I
old fever Ulceration of Peyer's patches Ileum Swelling of mesenteric lymph nds Acute splenic tumor Paren matous degeneration of kidneys liver l heart Chronic adhesive pleuritis ema of lungs	Weight 250 gm Organ flabby, soft and somewhat blood stained Epi and endocardium smooth Left ventricle has a grayish opaque appearance and collapses over ones fingers On tangential section this grayish opacity is more deeply marked	F
oid fever General peritonitis Perforation of gall bladder Hyperplasia and ration of Peyer's patches of lower part ileum Hyperplasia of mesenteric nph glands Acute splenic tumor nchymatous degeneration of liver and dneys Cholelithiasis Cystitis	Epicardium and endocardium smooth Muscle firm On section reddish brown in color and homogeneous throughout Here and there small gray points can be seen Coronary arteries normal and free from atheroma	N
oid fever Hyperplasia and ulceration Peyer's patches and solitary follicles Ileum Hyperplasia of mesenteric mph glands Acute splenic tumor nchymatous degeneration of liver and dneys Obesity Parenchymatous degeneration of heart muscle	Weight 420 gm Organ of large size Epicardium contains abundant fat Muscle firm in consistency reddish brown in color Somewhat cloudy Fresh plaques of sclerosis in coronaries	F
sons disease Congenital atrophy of henals Typhoid fever Tuberculosis of onchial lymph glands	Weight 170 gm Surface smooth Under epicardium of left ventricle several ecchymoses Muscle firm in consistency Compact in texture and of a brownish red color	F
hoid fever Hyperplasia of lymphatic ssue in intestine with sloughing in ileum nd upper colon Deep ulceration in lower leum Acute splenic tumor Hyperplasia t mesenteric and portal lymphatics loudy swelling of liver and kidneys	Not enlarged and muscle of rather grayish appearance Distinctly softer than normal	N
phoid fever Hyperplasia and necrosis of Peyer's patches of ileum Hyperplasia of solitary follicles of ileum cecum and ascending colon Swelling of mesenteric lymph glands Acute splenic tumor Fatty degeneration of liver Acute nephritis Chronic pulmonary tuberculosis at right apex Recent and healed laparotomy wounds Localized fibrinous peritonitis	Surface smooth Muscle firm brownish red in color Below epicardium numerous minute ecchymoses	F

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

Series No	Pathological No	Age	Sex	Color	Duration of Illness,	Cause of Death	Main Clinical Features
29	1618	27	M	W	3 weeks	Intestinal hemorrhage	Patient taken ill 3 weeks before admission with fever and chills During this time had wandered about streets sleeping in markets Had a large hemorrhage on morning of admission Was very ill when he entered hospital and evidently suffering from loss of blood After admission bled continuously from the bowel and died the following day No special circulatory symptoms
30	1630	21	M	B	16 days	Toxemia	After an illness of 7 days with fever, headache, nausea and some vomiting entered hospital Was very dull and ill on admission but in good general condition On 4th day developed pain and tenderness in right iliac fossa which increased in intensity and on the 7th day laparotomy was performed No intestinal perforation was found but an acute appendicitis with some fluid about the cecum Patient did well after operation until the 2nd day when his pulse rapidly rose to 160 and he gradually sank On admission and after first sound at apex was noted to have a murmurish quality No other unusual circulatory symptoms noted
31	1587	10	I	W	25 days	Hemorrhage Hemorrhagic typhoid without intestinal lesions	Entered hospital after being ill 5 days with headache and fever Patient was deeply intoxicated and on 5th and 6th days had vomiting On 12th day nosebleed began Bleeding from nose and mucous membranes of mouth continued uninterruptedly and patient had blood in stools and hemorrhagic spots in skin Became extremely anemic and died on 20th hospital day A very rapid weak pulse the only circulatory symptom On admission there was a systolic murmur at the apex
32	1576	19	M	W	29 days	Toxemia (?) Died after convulsions	Patient entered hospital after an illness of 1 week with headache fever and abdominal pain Symptoms of toxemia increased in severity Great muscular twitching developed and after several convulsions patient died on 22nd hospital day Throughout illness had considerable abdominal pain and tenderness suggesting perforation Pulse rapid and of small volume Heart sounds blurred and rhythm approached embryocardia
33	1575	20	M		26 days?	Peritonitis following intestinal perforation	Entered hospital complaining of epigastric pain Had been ill 12 days with fever and abdominal pain The abdominal symptoms became more marked and patient was operated on on the 7th day After operation grew gradually weaker and died on the 14th day Pulse rather slow No other circulatory symptoms
34	1452	46	M	W	65 days?	Exhaustion Death occurred suddenly	A prolonged attack of fever with intercurrent relapse Patient had been ill 6 weeks before admission with fever pain in chest and cough, although he remained at work On admission was thin and worn On 17th day developed left sided hemiplegia followed by stupor and Cheyne Stokes breathing On 23rd day died very suddenly Circulatory symptoms extremely prominent On admission signs of mitral insufficiency (systolic murmur and accentuation of pulmonic second sound) and a slow and very irregular pulse Pulse remained irregular throughout illness Before death gallop rhythm
35	1450						History lost

Anatomical Diagnosis	Description of Heart	
	Gross	Microscopical
Typhoid fever Many dirty-looking ulcers in the lower ileum and cecum Great swelling of Peyer's patches and solitary follicles Hemorrhage from bowel Cloudy swelling of mesenteric lymph glands heart muscles and kidneys Fatty liver Acute splenic tumor Fresh bronchopneumonia Fatty change in endothelium of aorta	Weight 240 gm Muscle soft and opaque Gray in color	The myocardial changes are extensive Fibers are granular and in places the striation is obscured Marked sarcoplasmic increase some fibers on cross section having fibril bundles only about the periphery In some areas the muscle cells have been completely destroyed Nuclear changes are marked Extensive diffuse and intense local areas of infiltration Large areas of infiltrating cells under the pericardium Edema of interstitial tissue Fresh (?) connective tissue formation Several old areas of connective tissue with fresh infiltration about them
Typhoid fever Ulcers in ileum and colon Hyperplasia of mesenteric lymph glands Acute splenic tumor Parenchymatous degeneration of kidneys	Weight 300 gm Myocardium flabby, opaque, of a pale yellowish color	Marked fiber changes Nuclear changes extensive Considerable sarcoplasmic increase Marked fragmentation Some vacuolar degeneration and in places a few fibers are completely degenerated The interstitial lesions are definite but not nearly so intense as in other cases The cells are mostly small and large round cells with eccentric nuclei Hemorrhage into muscle Some chronic thickening of arterial walls
Typhoid fever without intestinal lesions Hyperplasia of lymph glands Acute splenic tumor Anemia subcutaneous and subserous ecchymoses	Weight 120 gm Numerous ecchymoses on epicardium Muscle pale brown in color On section are seen a few ecchymoses in muscle substance Muscle is firm Numerous ecchymoses on endocardium	Most extensive fiber and interstitial lesions Marked sarcoplasmic increase Many fibers show marked vacuolization Nuclear changes marked No special fragmentation Many muscle fibers have undergone complete disintegration leaving degenerated nuclei The interstitial changes are extensive and intense Areas of infiltration under pericardium and throughout the muscle A striking feature is the large number of eosinophils Marked hemorrhage into muscle and edema
Typhoid fever Numerous superficial ulcerations in lower part of ileum, in cecum and in rectum Older ulceration in the cecum Enlarged mesenteric glands Acute splenic tumor Fatty degeneration of liver and of intima of aorta Cloudy swelling of myocardium and of kidneys Fresh bronchopneumonia	Weight 225 gm Pericardium normal Muscle of opaque, reddish brown color Somewhat soft	Nuclear changes moderately well marked Fibers look granular In papillary muscle considerable sarcoplasmic increase but none elsewhere Cement lines prominent No definite fragmentation Numerous areas of cells under epicardium but no large areas of infiltration Connective tissue spaces rich in cells but no large accumulations
Typhoid fever Swelling and ulceration of Peyer's patches and solitary follicles Perforation of typhoid ulcer Fibrinopurulent peritonitis Acute splenic tumor Hyperplasia of mesenteric lymph glands Ulcers of stomach Acute nephritis	Weight 270 gm Muscle quite firm in texture Brown in color	Nuclear changes well marked "Cement lines" apparent and occasional fragmentation No interstitial change
Typhoid fever Healed ulcers in intestines Moderate splenic tumor Thrombosis of left iliac and femoral veins Embolism of vena cava inferior Parietal thrombi in left ventricle Embolism of smaller pulmonary arteries Infarction of right lung Bronchopneumonia Anemic infarcts of kidneys Fibrinous pleuritis Infarction of spleen Tuberculosis of cervical lymph glands	Weight 620 gm Valves normal except mitral shows slight thickening Right auricle and ventricle greatly dilated and marked thickening of right ventricle Left auricle and ventricle somewhat dilated and papillary muscles flattened Several firm thrombus masses between trabeculæ Muscle soft and flabby On tangential section shows mottling	Marked nuclear changes Pigmentation Slight fragmentation Fibers show sarcoplasmic increase and some vacuolization In small areas the fibers seem to be undergoing complete degeneration Numerous areas of interstitial infiltration some beginning under epicardium others in the connective tissue bands Cells small and large mononuclears with some polymorphonuclears and large cells with eccentric nuclei Areas of chronic fibroid change with fresh infiltration
Typhoid fever Ulceration of Peyer's patches and solitary nodules in ileum and colon Acute splenic tumor Parenchymatous degeneration of kidneys and liver Ulcers in larynx Pulmonary infarct and edema Hyperplasia of esophageal lymph glands Gastric and intestinal hemorrhages Hemorrhagic diathesis	Heart muscle pale feels soft	Moderate nuclear changes and pigmentation Some fragmentation Fibers look granular No interstitial changes

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

Series No	Pathological No	Age	Sex	Color	Duration of Illness	Cause of Death	Main Clinical Features
36	1439	20	F	B	28 days	Acute lobar pneumonia	Ill for 18 days with fever headache and abdominal pain before admission to hospital On day of admission and subsequent 3 days blood in stools amounting in all to about 1 liter On 3rd day patient developed lobar pneumonia and general condition became progressively worse to time of death on 14th day Heart sounds feeble and pulse occasionally irregular Later first sound reduplicated at apex
37	1437	17	M	B	25 days	Toxemia Died rather suddenly	Ill for 16 days before admission with fever and feeling weak and miserable Patient had a very high temperature and later became deeply intoxicated On 2nd day after admission, embryocardia pulse very rapid and at times irregular
38	1432	21	M	W	16 days	Peritonitis following intestinal perforation	Onset 12 days before admission with headache general malaise and fever On 4th day patient developed an abscess in left submaxillary gland which was incised On 17th day had small hemorrhage followed by symptoms of perforation and general peritonitis Sank rapidly and died on 24th day Systolic murmur at apex with marked accentuation of both second sounds
39	1415	25	M	B	16 days	Peritonitis following intestinal perforation	Patient entered hospital in good general condition after having been ill 2 weeks with fever weakness and nausea On 3rd day symptoms of perforation and operation the same day 2 days later a second operation for general peritonitis followed in 10 hours by death Soft systolic murmur at apex with accentuation of second pulmonic sound
40	1320	40	M	W	13 weeks? History of onset is indefinite	Toxemia	Patient ill for 10 weeks before admission with stomach trouble and chills and fever Condition fairly good but mind wandering Patient has an extensive pleurisy on left side phlebitis of right popliteal vein After admission had a number of chills followed by profuse sweating Jaundiced on admission and remained so to time of death Toward end breathing became labored and patient cyanotic Pulse gradually failed Last few days of life pulse was irregular Second pulmonic sound accentuated No murmurs
41	1175	28	M	W	24 days	Toxemia	Onset 10 days before admission with fever, headache and diarrhea In good condition on admission but later became deeply intoxicated with marked subsultus and rigidity of arms and legs Severe nosebleed on 13th day followed by blood in stools On admission heart sounds clear but later a systolic murmur developed with accentuation of the second pulmonic sound Toward end pulse became small and thready and very irregular Patient was deeply cyanosed and developed Cheyne Stokes breathing
42	1147	31	M	B	27 days	Peritonitis following intestinal perforation	Entered hospital in good general condition after an illness of 12 days with fever and headache On 5th day had abdominal pain and there were indefinite signs of perforation On the 15th day the signs became prominent Operation on 17th day followed by death on the 16th Heart sounds described as being faint and distant and the first sound at apex as of an indefinite quality
43	1117	21	M	B	23 days	General staphylococcus infection	Onset of illness 9 days before admission with headache and pain in limbs and weakness Patient in good general condition on admission but later became irrational and drowsy and dull On 9th day there was pain and marked swelling of right parotid gland which was opened and drained on the 11th Patient grew gradually worse and died on the 13th day No circulatory symptoms other than the first sound having a murmurish quality

Anatomical Diagnosis	Description of Heart — Gross	Description of Heart — Microscopical
Typhoid fever Hyperplasia ulceration and necrosis of Peyer's patches and solitary follicles Acute enlargement and necrosis of mesenteric glands Acute croupous pneumonia Pulmonary edema Cloudy swelling of liver and kidneys Acute splenic tumor Chronic adhesive peritonitis Chronic adhesive pleuritis Acute fibrinous pleurisy	Weight 200 gm Muscle pale and almost pure brown in color	Fibers in places are granular Marked nuclear changes Moderate sarcoplasmic increase Extensive fragmentation Small accumulations of cells under epicardium and about blood-vessels No infiltration Hemorrhage into muscle
Typhoid fever Ulceration in colon and lymphatic hyperplasia Ulceration in ileum Hyperplasia of mesenteric lymph-glands Acute splenic tumor Cloudy swelling of liver and kidneys Slight bronchopneumonia and atelectasis Old pleural adhesions	Weight 395 gm Few small ecchymoses on posterior surface	Nuclear changes marked Pigmentation moderate Cement lines" prominent but no fragmentation Sections not very satisfactory
Typhoid fever Ulcers in the ileum Perforation of an ulcer Generalized peritonitis Acute splenic tumor Hyperplasia of mesenteric lymph glands Suppurative inflammation of left submaxillary gland Bronchopneumonia with abscess formation	Valves are delicate and compensate Muscle appears slightly softened and is rather opaque and cloudy in appearance	Fibers look granular Nuclear changes and pigmentation marked Marked sarcoplasmic increase No fragmentation Areas of infiltration under epicardium and rather extensive infiltration in papillary muscle Artery walls somewhat thickened and there are areas of apparently chronic fibroid change with fresh infiltration about them
Typhoid fever Ulceration of ileum and perforation of intestinal wall Acute general fibrinopurulent peritonitis Acute splenic tumor Hyperplasia of lymphatic glands Cloudy swelling of liver and kidneys	Weight 250 gm Pericardium slightly congested Valve margins clear	Fibers a little granular Nuclear changes very well marked and moderate pigmentation No sarcoplasmic increase No vacuolization Slight fragmentation No interstitial changes
Typhoid fever (healing ulcers) Acute splenic tumor with infarctions Chronic aortic endocarditis Chronic diffuse nephritis Slight bronchopneumonia Adhesions between diaphragm and left lung and spleen	Pericardium smooth and glistening Aortic valves somewhat thickened Two coronary segments bound together Muscle very soft and flabby	Fibers are granular Marked nuclear changes and extensive fragmentation Considerable sarcoplasmic increase Capillaries unusually full of leukocytes but not interstitial infiltration
Typhoid fever Medullary swelling of lymphatic tissue in intestine Slight ulceration and swelling of mesenteric lymph glands Acute splenic tumor Hemorrhage into intestinal canal Chronic adhesive perienteritis Chronic pleuritis	Pericardium adherent over whole heart by veil-like adhesions Heart weight 310 gm All valves delicate and competent Endocardium smooth Myocardium apparently normal	Fibers in places granular and striation obscured Nuclear changes marked Cement lines evident but no separation Some sarcoplasmic increase but this feature not marked Several areas of rather extensive infiltration especially in papillary muscle Many large nests of infiltration under the epicardium Many of the characteristic cells found in all the cases with infiltration but especially predominating in Case 27
Typhoid fever Intestinal perforation General fibrinopurulent peritonitis Healing ulcers in ileum, cecum and appendix Slight ileocolitis Suppurating peritoneal glands Acute splenic tumor Cloudy swelling of kidneys	Weight 250 gm Muscle a little opaque firm apparently but little altered from normal	No marked changes other than the nuclear which are large and swollen and distorted Some segmentation Areas of small round cells under the pericardium and throughout the connective tissue spaces but no definite infiltration between muscle fibers
Typhoid fever Swelling and superficial ulceration of follicles of small and large intestines Diffuse hemorrhagic infiltration of mucous membrane of intestines Distention of gall bladder with pericystic inflammation Liver abscess and necrosis Abscess of gastrohepatic lymph glands Multiple lung abscesses Bronchopneumonia Acute fibrinous pleurisy Multiple kidney abscesses Acute splenic tumor Parenchymatous degeneration of kidneys Suppuration of parotid glands	Weight 320 gm Pericardium and epicardium smooth Valves delicate Consistency of heart's flesh firm	Fibers are granular and in some striation obscured Nuclear changes marked Cement lines prominent but no fragmentation Only moderate sarcoplasmic increase Numerous areas of infiltration under the epicardium and endocardium Infiltration of muscle particularly marked in papillary muscle

THE FUNCTIONAL DISTURBANCES IN PAROXYSMAL TACHYCARDIA

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In studying the attacks of tachycardia which have been known since the description of Cotton in 1867 and which Bouveret has designated as "essential" or "idiopathic" paroxysmal tachycardia, it is necessary to distinguish very carefully between "paroxysms of tachycardia" and idiopathic paroxysmal tachycardia In the ordinary tachycardias of emotion, excitement or exercise, the pulse-rate gradually quickens and finally reaches its maximum, and when the cause is over the rate subsides gradually In the idiopathic paroxysmal tachycardia the rate rises and falls suddenly The heart-beats just preceding the paroxysm have the usual rate With the second beat of the paroxysm the heart-beat is already about double that of the preceding and has reached the maximal rate of the paroxysm The rate then continues practically unchanged throughout the paroxysm, and without warning the paroxysm subsides as suddenly as it has come

This sudden onset and sudden subsidence is quite unique and distinct from the ordinary effects of the cardiac nerves The changes of rate from stimulation of the cardiac nerves from emotion, excitement or exercise never are so sudden Their mode of action is typified by a patient who, during a year after an attack of typhoid fever was subject to attacks of palpitation and rather sudden onsets of tachycardia so that there was a suspicion of idiopathic paroxysmal tachycardia At the beginning of the examination his pulse was 60 per minute As I began to get the cardiosphygmograph ready, he became excited and in successive quarters of a minute his pulse-rate rose from 15 to 20 to 25 and in the last quarter of a minute to 30 Within one minute the pulse-rate had doubled but the change of rate was gradual and not sudden It was evident that this was not idiopathic paroxysmal tachycardia and the subsequent history of the patient proved conclusively that it was not

The views of the older writers, that paroxysmal tachycardia is the result of a vagus neurosis seem to be disproved Gerhardt and later Hirschfelder have shown that paroxysms cannot be produced in patients by paralyzing the vagi with atropin between attacks and even stimulating the accelerator nerves by exercise while the patient's vagi are

paralyzed with atropin, fails to bring on an attack Moreover, S Hyman, working under Sir Victor Horsley, has produced lesions of the vagus nuclei in the medulla in a large series of dogs and monkeys, but this has never given rise to paroxysmal tachycardia It is evident, therefore, that another mechanism must be sought

The venous tracings taken from patients with paroxysmal tachycardia have shown two types and a number of cases of each have been reported (1) the auricular type, in which the auricular presystolic (*a*) wave is preserved throughout the attack, and (2), the ventricular type, in which the *a* wave is absent from the venous pulse

It would appear from clinical manifestations and experimental evidence that these two types represent merely different grades in the intensity of the same condition and not the result of totally different causes

The cause of this change probably lies not in the extracardiac nerves, but in an increased irritability of the heart-muscle, or, if the neurogenic theory is adopted, in the nerve-endings within the heart-muscle Although such changes in rate have never been observed from stimulation of nerves, they have been produced by increasing the irritability and rhythmicity of the muscle Ludwig and Hoffa in 1849 and, since then, numerous other observers have demonstrated that weak faradization of the mammalian heart gave rise to a sudden increase in the heart-rate, while strong stimulation caused fibrillation Hirschfelder has shown that this increase in rate amounts to an almost exact doubling, and that it comes on absolutely suddenly, just as is found in paroxysmal tachycardia It also subsides suddenly, within the space of a single beat, which still further bears out the parallelism (Fig 3A and B)

The exact effect of such faradization varies with the intensity of the stimulus and with the irritability of the heart If the stimulus is a very weak one there is no doubling of the rate, but there are occasional extrasystoles The extrasystoles may even accompany every alternate beat and give rise to a continuous bigeminal pulse

If the stimulus is increased very slightly, the first effect observed is a sudden approximate doubling of the rate of the auricles (Fig 1) The ventricles follow each auricular beat but the conduction time during the paroxysm is definitely longer than at the normal rate, that is, the conductivity is diminished during the paroxysm (Fig 2)

Most of these paroxysms however last only as long as the faradization itself and the heart rate returns to normal, as soon as the stimulation is stopped

If the faradization is repeated several times in rapid succession or if the intensity of the stimulus is increased, or on the other hand if the irritability of the heart is of high grade, the auricles and ventricles may contract absolutely synchronously (Fig 3)

Since it is difficult to conceive that conduction from auricle to ventricle would be so rapid as to occupy an almost infinitesimal time it may be assumed with Hering and Mackenzie, that in this case the cardiac impulse arises in the Purkinje fibers of the auriculoventricular bundle and is conducted simultaneously in both directions, a condition which Mackenzie terms a "nodal rhythm"

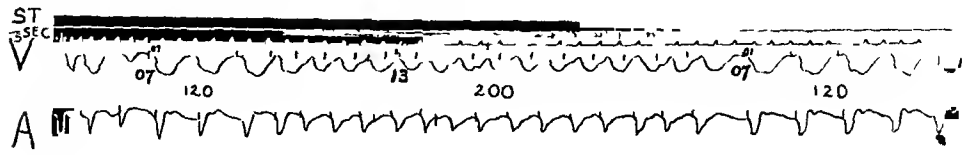

Fig 1—Mild faradization of the auricle Tachycardia with slowed conduction, lasting as long as the stimulation Downstrokes = Systole, time in 1/5 seconds A = auricular contractions, V = ventricular contractions St = stimulation of auricle

Rhythms of this type have been demonstrated by Matthews and by Cushny after aconite poisoning but it is not possible to prove absolutely that in the mammal they originate in the cells of the auriculoventricular bundle Dr G S Bond, in my laboratory has recently bridged this gap by studying the effects of aconite poisoning in the frog's heart He has found that in the frog's heart one can watch the ring of muscle at the auriculoventricular junction contract Normally it contracts just after the auricle and just before the ventricle but in aconite poisoning one occasionally encounters extrasystoles in which the auriculoventricular ring contracts first and this is followed by the systole of the auricles and ventricle which contract at the same instant The simultaneous-

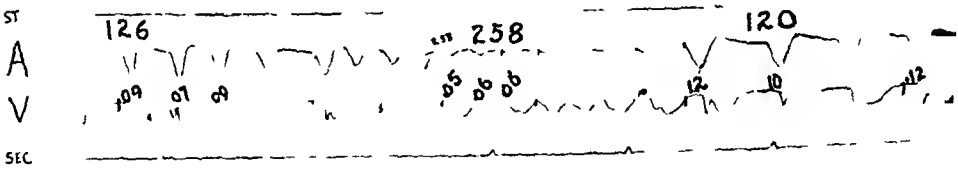

Fig 2—Slightly more intense stimulation Tachycardia with quickened conduction outlasting the period of stimulation Time in seconds

contractions of auricle and ventricle in the mammal seem exactly similar to this and hence are assumed to be auriculoventricular in origin

If the faradic stimulus is still more intense, the auricles pass at once into fibrillary contractions, and the ventricles respond with a sudden doubling of the rate, sometimes regular and sometimes irregular, which is almost exactly the same rate as that which occurs when the auricles are undergoing coordinate contractions at the doubled rate (Fig 4)

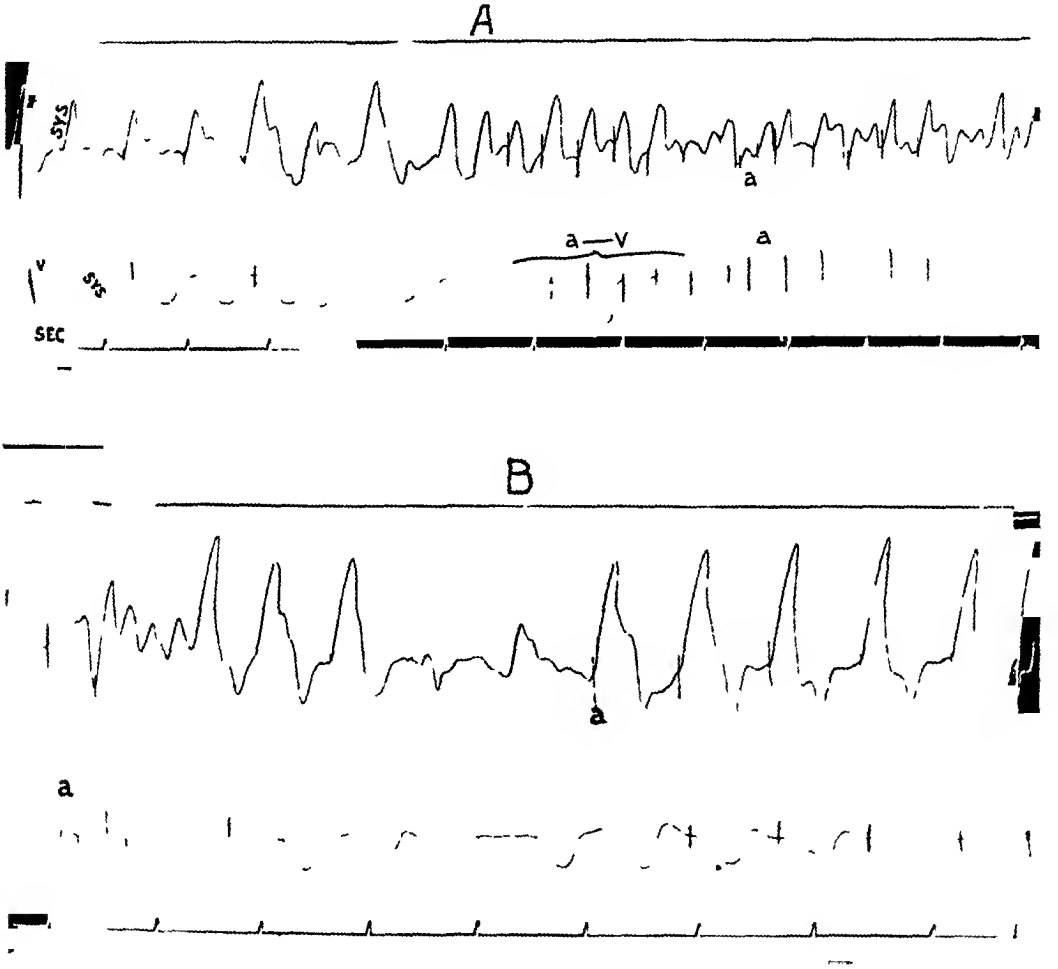

Fig 3—Effect of more intense stimulation A, onset of paroxysm, B, subsidence of paroxysm Tracing of auricular contractions made by the suspension method (upstrokes = systole) that of ventricles by tambour transmission (downstrokes = systole) A short series of simultaneous contractions of auricles and ventricles (auriculoventricular rhythm a v) is terminated by an auricular extrasystole (a) after which the auricle initiates the rhythm Auricles (a) upstrokes = systole Ventricles (v), downstrokes = systole

The electrocardiogram shows that the fibrillating auricles give rise to very numerous stimuli at an irregular rate of from 300 to 900 per minute too fast for the ventricles to follow but the intensity of each electrical variation is of almost the same magnitude and is sometimes even

greater than that of a normal impulse MacWilliam and later Hirschfelder have shown that, when stimuli are thrown into the heart too fast for it to follow, it frequently responds by a doubling of the rate rather than by a contraction in response to each individual stimulus and the rapidly recurring stimuli from the fibrillating auricles present exactly these conditions The auricular fibrillation and the ventricular tachycardia cease abruptly sometimes spontaneously sometimes after stimula-

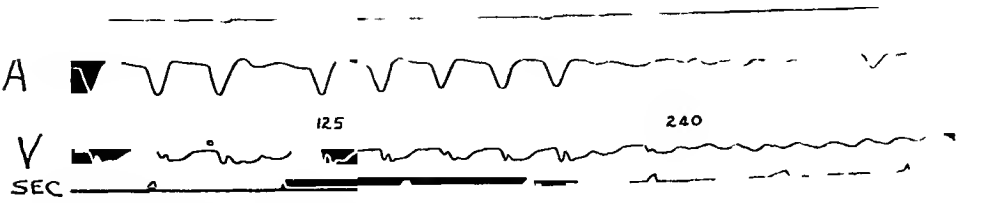

Fig 4—Still more intense stimulation Fibrillation of the auricle sets in, and is accompanied by tachycardia of the ventricle Downstrokes = systole

tion of the vagi (Fig 5) Sometimes the tachycardia resists the vagus stimulation and persists in spite of it (Fig 6)

Besides these conditions fibrillation of the auricles with the accompanying tachycardias have been produced experimentally in several ways

Garrey and Hewlett produced it after the cessation of vagus stimulation but only when the heart had already been in a state of greatly increased irritability Cushny and Edmunds, who were the first to associate it with paroxysms of arhythmias, though not with paroxysmal tachycardia obtained fibrillation in many animals poisoned with morphin Thomas Lewis has recently produced such attacks of auricular fibrillation and

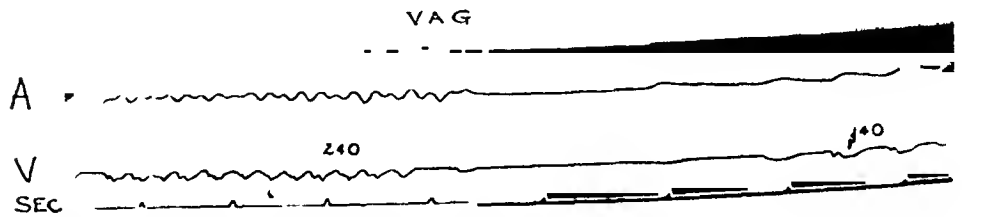

Fig 5—Effect of stimulation of the vagus (vag) on a mild paroxysm bringing about cessation of the tachycardia

ventricular tachycardia in dogs about an hour after ligature of the right coronary artery thus simulating the association of coronary sclerosis and paroxysmal tachycardia to which Romberg has called attention The fact that paroxysmal tachycardia is a disease common in otherwise healthy children and in the young and that it often lasts from thirty to fifty

years would indicate that coronary sclerosis is not the usual etiologic factor

In this series of experiments Lewis has reproduced experimentally all the forms of auricular, auriculoventricular and ventricular tachycardias which one can obtain by faradic stimulation and has furnished further evidence for the belief that they are all to be regarded as transitional forms of the same general disturbance

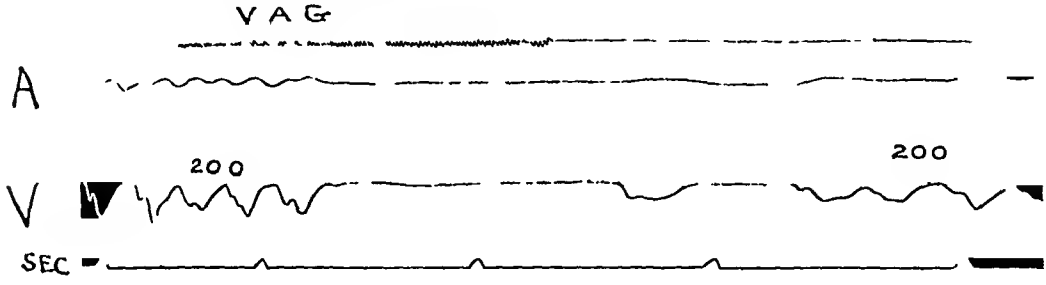

Fig 6—Effect of stimulation of the vagus upon a severe paroxysm, causing temporary stoppage The tachycardia is then resumed

Moreover, Cushny has recently produced all these forms of cardiac action in aconite poisoning

The question is, therefore, how the experimental findings explain the clinical It is quite evident that in suddenness of onset and cessation, in the form of venous pulse in the partial independence of vagus control the experimental paroxysms resemble the clinical The resemblance could be absolutely clinched by means of the electrocardiogram

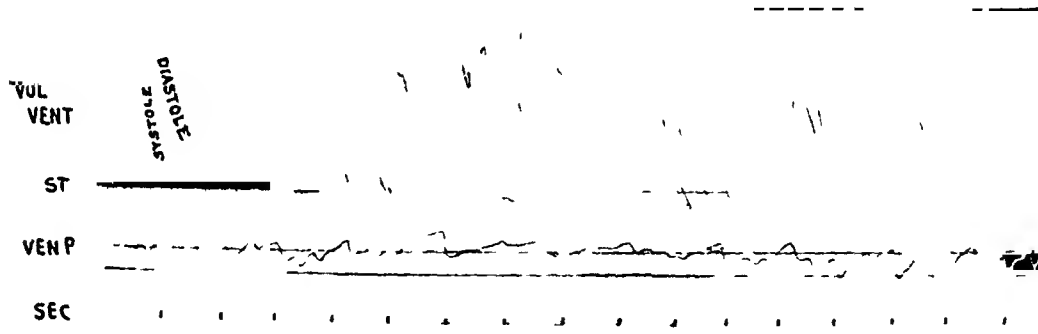

Fig 7—Diminution in the volume of the ventricles and rise of venous pressure in experimental paroxysmal tachycardia Vent Vol = volume of the ventricles Ven P = venous pressure St = stimulation of the ventricles with induction shocks

Thus far a few satisfactory electrocardiograms have been made by Thomas Lewis but only in cases of the first type with auricular contractions well marked on the venous pulse In these he has found, of course well-marked auricular (P) waves on the electrocardiogram, and

consequently has concluded that auricular fibrillation is not a factor in paroxysmal tachycardia Apparently he has entirely overlooked the cases of the second type, with the ventricular venous pulse These are often the severest cases, and in them, from analogy with his other cases of ventricular venous pulse, as well as from the experimental results one would expect to find evidences of auricular fibrillation

Most of the symptoms of paroxysmal tachycardia seem to be referable to the disturbances in the distribution of the blood within the vessels As will be seen in the tracing (Fig 7) very much less blood enters the heart in the short diastoles and consequently the blood stagnates in the veins and the venous pressure rises Occasionally, in man it rises to 26 cm of water, as recorded by Hooker and Eyster, about as high as in broken compensation, so that the veins of the neck become distended and pulsate, and the liver swells, and even edema may set in

When the attack subsides there is a sudden inrush of blood into the heart which distends the heart and gives rise to the anginal symptoms that are so common at the termination of the attack

As will be noticed, so little blood enters the ventricles during the attack that very little can be put out at each systole and consequently the blood-pressure falls and the patient suffers from weakness giddiness and muscæ volitantes, and occasionally even fainting spells all the result of depletion of the arteries and of cerebral anemia

Dietlen and other observers with the x-ray found that the hearts of patients often became smaller during the attacks In the volume curves taken in the experimental paroxysms will be noticed that the same thing has taken place The underfilling of the heart causes its total volume to diminish very much It is seen therefore that in both the clinical condition and its experimental simulation there is the absolutely abrupt onset and abrupt cessation of an intense tachycardia associated with a great increase in the irritability of the heart during which the cardiac impulse may originate in any of several different ways that the milder attacks of this tachycardia may sometimes be stopped by influences which stimulate the vagi but the severer ones cannot and hence they cannot be reached by our ordinary therapeutic measures that the mere tachycardia itself prevents the adequate filling of the heart thus bringing about symptoms due to venous stasis and symptoms due to cerebral arterial anemia and that the inrush of blood at the end of the paroxysm gives rise to cardiac dilatation which causes the feeling of intense constriction at the termination of the attack

In other words, the picture produced in the laboratory simulates and accounts for the clinical picture, the physical signs, and the symptoms of the patient

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AN EXPERIMENTAL STUDY OF THE PHARMACOLOGY OF ERGOT

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This research was started as an investigation of the quality of ergot which is at present on the market, and to find a means of improving it For the purpose of determining the quality of ergot in the light of the knowledge of the chemistry of this subject, the only method which seemed available was the physiological test, but from the beginning, we were impressed with the desirability of establishing if possible, a chemical method for the standardization of this drug The biological assay of drugs is commercially possible only for large manufacturing houses, since it involves the necessity of employing a separate expert and even under the best conditions, can never be regarded as more than approximately accurate, whereas the proper chemical test should, at least theoretically, be reliable within a very small limit of error As a result of our studies, we have finally developed a chemical method for the assay of ergot, which in our opinion, is more reliable than any physiological test for this drug which has ever been suggested For a proper understanding of the basis of the methods we shall suggest and of the evidence of their reliability, it is necessary that we go into the question of the physiological effect of ergot and of the nature of its active principle Therefore, we shall divide the paper into four sections 'The Physiology of Ergot,' "The Chemistry of Ergot "The Biological Assay' and "The Chemical Assay' In the two introductory sections it is not our intention to consider in detail the work which has been done on the physiology and chemistry of this drug but to present chiefly the experimental results of our own investigations

THE PHYSIOLOGY OF ERGOT

The use of ergot in medicine may be dated from the paper of Stearns[1] in which attention was directed to the stimulating influence of the drug upon the uterine muscles In 1870 Holmes[2] demonstrated that the intra-

* A part of the expenses of this research was defrayed by a grant from the American Therapeutic Society

* From the Laboratory of Pharmacology University of Pennsylvania

2 Holmes Arch de physiol norm et path 1870 iii

1 Stearns New York Med Repository 1807

venous injection of the drug gave rise to a marked rise in the blood-pressure which he attributed to vasomotor constriction In 1906 Meltzer and Auer found that ergot increased the activity of the intestinal muscles and in the same year, Dale[3] showed that a similar effect was exercised on practically all the unstriped muscles of the body There can be

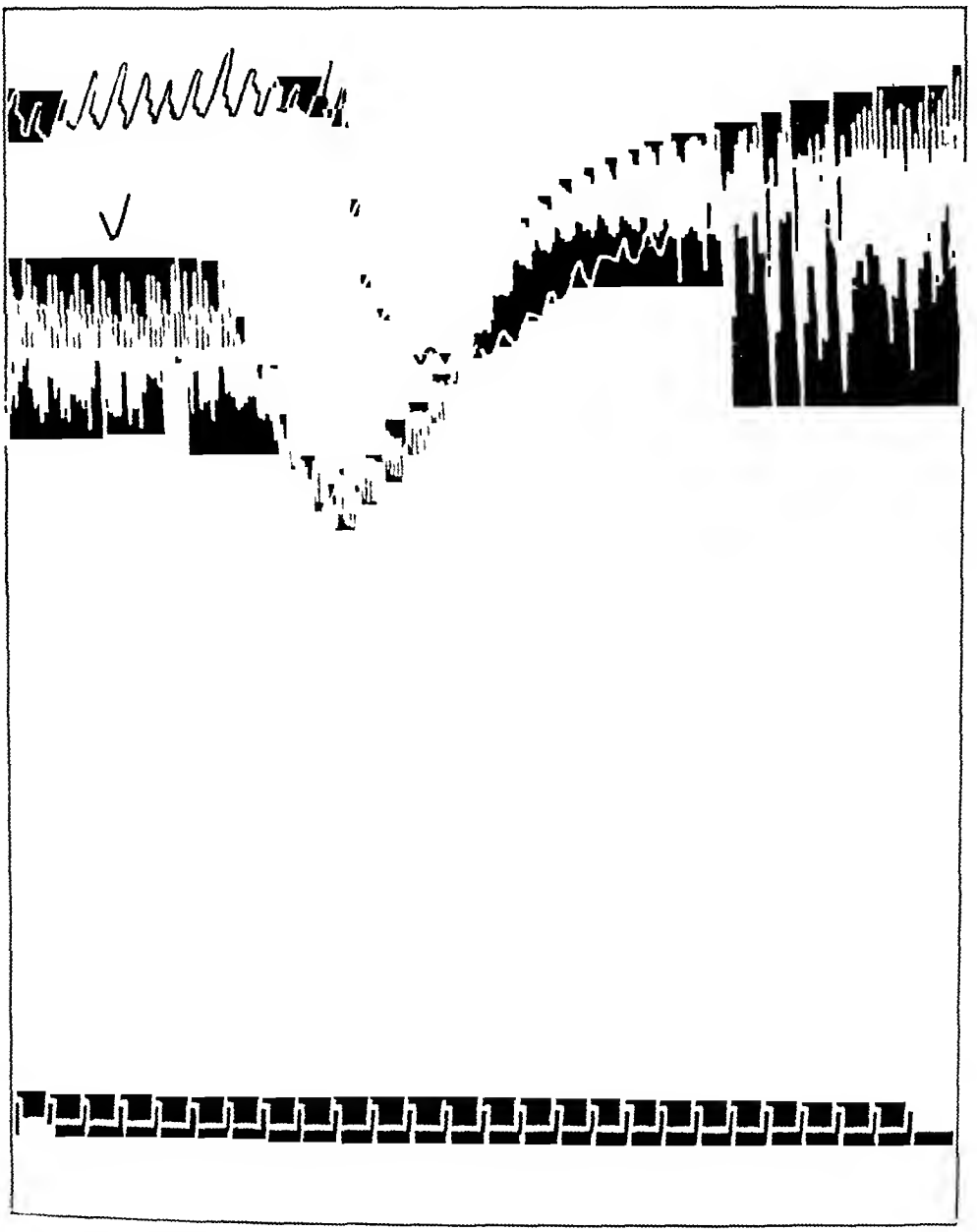

Fig 1 Showing effect of ergot on blood pressure and kidney volume At arrow injection of 0 16 gm per kilo Time marker = 5 seconds

little doubt but that the increased contractions of the uterus and the vasomotor stimulation are part of a wide-spread effect of the drug involving all involuntary muscle

[3] Dale Journ Physiol 1906 xxxiv 163

There has been some difference of opinion as to whether the stimulant influence on the muscle is the result of an action on the nerve centers or a peripheral effect, either on the terminals of the nerve or the muscle itself. Hemmeter[4] was unable to obtain any evidence of a stimulant

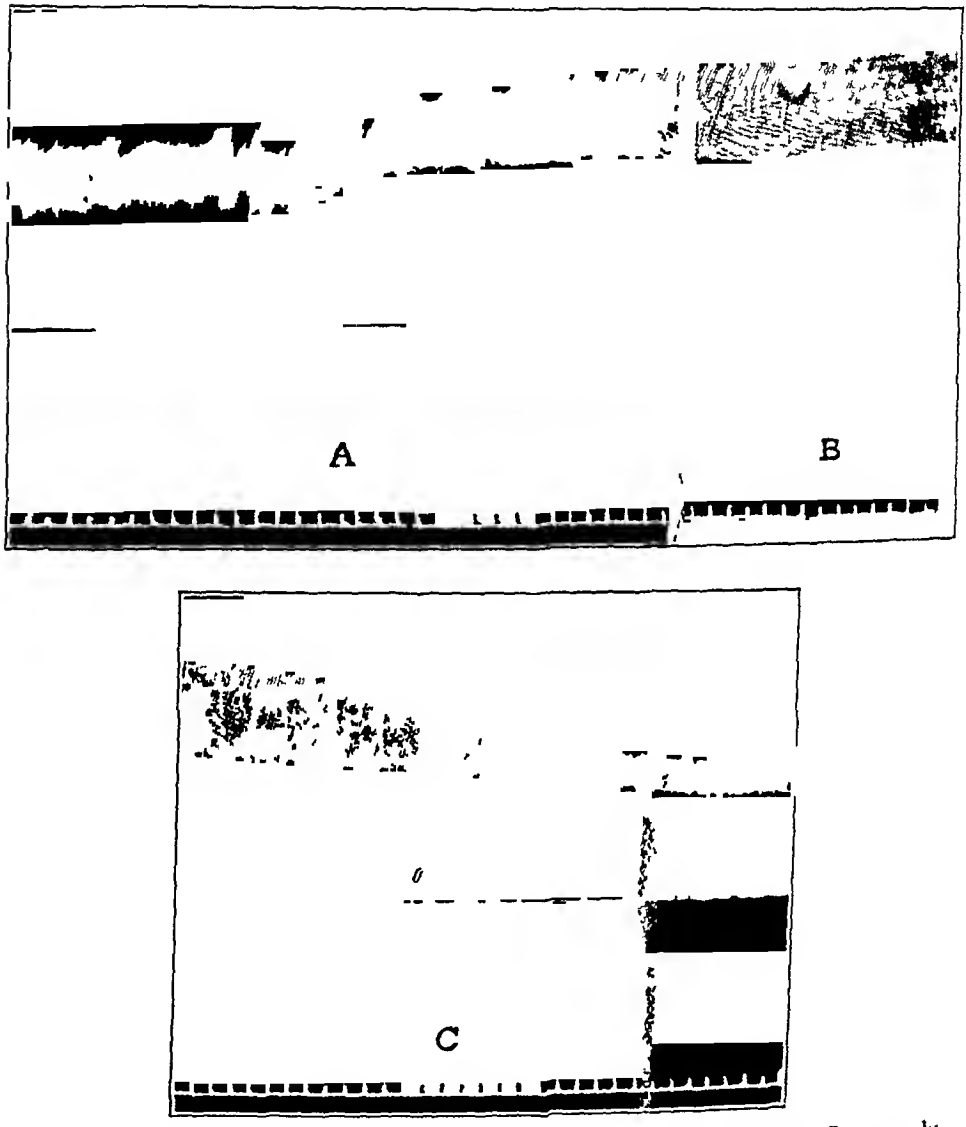

Fig. 2.—Showing increase of pulse pressure caused by ergot. Tracing by Hurthl's manometer. Both vagi have been cut. At V. injected 0.16 gm. per kilo. Interval between A and B, 3 minutes (0.32 gm. ergot); between B and C, 6 minutes. Time marker = 2 seconds.

influence on either the uterus or the vascular system after destruction of the spinal cord. Wood[5] also reached the conclusion that ergot did not

4 Hemmeter, Med. News, Philadelphia, 1891, lxii.
5 Wood, Philadelphia Med. Times, 1874, iv, 518.

produce a rise of pressure after destruction of the vasomotor centers These authors concluded, therefore, that the action of ergot was central On the other hand, the experiments of Dixon, of Dale and others seem to demonstrate clearly that the destruction of the medulla does not prevent the action of the drug on the circulation, and Kehrer[6] found that isolated strips of uterine muscle were stimulated by ergot

In our own experiments, we have found that the rise of pressure after destruction of the vasomotor centers was even greater than in the normal animal For the purpose of excluding central vasomotor effects, we have used two methods which yielded similar results The first is the common method of cutting the spinal cord in the cervical region, and the second which we prefer because there is no loss of blood, is that described in a paper by Asher and Wood,[7] of injecting paraffin into the internal carotid artery with sufficient force to block the circle of Willis and the vertebral arteries so that the vital centers are killed by acute anemia In Table 1 are presented the results of two of these experiments

Most authors have laid considerable stress on the primary fall of blood-pressure which occurs after the intravenous injection of a preparation of ergot, and Holmes attempted to argue from this the occurrence of constriction of the pulmonary vessels

TABLE 1—RESULTS OF TWO EXPERIMENTS ON EFFECT OF ERGOT ON CIRCULATION, EXCLUDING CENTRAL VASOMOTOR EFFECTS

Time*	Pressure	EXPERIMENT 1—PARAFFINED MEDULLA
0	73	Inject 0 30 gm per kilo fluidext ergot Squibb No 2
2	153	
5	184	
10	167	
25	143	
		Post mortem showed circle of Willis and both vertebral arteries completely filled with paraffin

Time	Pressure	EXPERIMENT 2—CUT CORD
0	91	Inject 0 20 per kilo fluidext ergot Squibb No 2
½	65	
1	140	
3	156	
5	150	
10	150	
20	159	
30	147	
		Post mortem showed cord completely severed between first and second cervical vertebræ

* Throughout this paper the column headed 'Time means minutes since beginning of the experiment and 'Pressure means millimeters of mercury

6 Kehrer Arch f exper Path u Pharmakol 1909 xlix 266
7 Asher and Wood Ztschr f Biol 1899 xix 307

In our experiments, the primary fall of blood-pressure has not been a constant phenomenon We have observed it frequently and almost regularly with doses equivalent to more than 0 3 gm per kilo When however, the dose does not exceed 0 16 the pressure-fall almost never occurs, and after hypodermic administration of the drug, we have not observed it In our opinion, it cannot be regarded as a part of the physiological action, but is really a poisonous effect from the use of too large doses

Our plethysmographic studies have shown a contraction of the vessels of the kidney and an enlargement of those of the limb The latter does not always occur and is probably passive in origin due to the blood forced out of the more powerful vascular areas by the high pressure

Recently Dixon has stated that ergot has a stimulant influence on the cardiac muscle as well as upon the arterial muscles The article in which we saw this statement contains no experimental evidence of its truth and we have been unable to find the data on which the conclusion is based We are, however, inclined to accept its truth, although our experimental data on the point are not conclusive After section of the pneumogastric nerve, we find that the pulse-pressure as measured by a Hurthl manometer is very greatly increased by the physiological dose of the drug and that after toxic doses the size of the pulse-wave increases and decreases as the blood-pressure ascends and, later, falls We have attempted to confirm this belief by studies on the isolated heart but our results so far, have not been definitive

One other point which requires mention as bearing on the elaboration of a means of physiological assay is the duration of the vasomotor constriction Cronyn and Henderson* state that the most prolonged rise of blood-pressure they have ever observed following the injection of ergot, lasted but forty minutes we have however in a number of experiments found the effects to last much longer The longest we have observed is a little over two hours, but as the experiment was not continued and the pressure was still decidedly above the normal it is fair to conclude that the effect is an enduring one Our explanation of the comparatively short duration of the vascular stimulation sometimes encountered is improper dosage If the dose be too small it is evident that we cannot expect the full physiological action of the drug and on the other hand if the dose is too large the toxic depressant action becomes manifest and forces the blood-pressure down In the latter instance the pressure generally but not always falls decidedly below the normal

* Cronyn and Henderson Jour Pharmacol and Exper Therap 1909 1 207

ACTIVE PRINCIPLE

It is not our intention to go into the history of the search for the active principle of ergot, as it has been well summed up by a number of previous writers, but only to mention briefly a few points which bear directly on certain new facts which we have to offer on this subject

In 1875, Tanret[8] described a crystalline alkaloid which he named ergotinin This was subsequently, however, shown to be physiologically inert In 1884, Kobert[9] ascribed the activity of ergot to two principles, one of which was a resinous acid which he called sphacelinic acid, and the second an alkaloid to which he gave the name of cornutin (It may be noted in passing that the cornutin of Keller is an entirely different body, probably a mixture of ergotinin and hydro-ergotinin) More recent investigations, however, have thrown doubt on the natural occurrence of cornutin and it is probably a decomposition product, which does not occur as such in ergot, and sphacelinic acid is not a pure proximate substance Jacobi[10] found in ergot a non-nitrogenous body which was neither an acid nor a glucosid, and was highly active physiologically This body to which he gave the name of sphacelotoxin, he regarded as the active ingredient of Kobert's sphacelinic acid He believed that it was found in ergot in the form of two loose combinations, in one with an acid body (chrysotoxin), in the other with an alkaloid (secalintoxin) In 1906 appeared two articles, one by Kraft,[11] the other by Barger and Carr,[12] describing a new alkaloid, to which the latter investigators gave the name of ergotoxin, but which Kraft showed to have the same empirical formula as ergotinin plus one molecule of water, and therefore named hydro-ergotinin Barger and Dale,[13] in their earlier communications claimed that the activity of all the substances which had been suggested as the active principle of ergot was due to contamination of these substances with ergotoxin which is an extremely powerful stimulant Recently however they have found that para-hydroxyphenylethylamin a principle which Barger and Walpole had previously separated from putrid meat infusions, occurs in ergot and has a similar action to the hydro-ergotinin The substance clavin isolated by Vahlen[14] and claimed by this investigator to be a uterine stimulant, has been shown by Dale and also by Cushny[15] to be inert

8 Tanret Compt rend Soc biol 1875 lxxxi 896
9 Kobert Arch f exper Path u Pharmakol 1884 xviii 316
10 Jacobi Arch f exper Path u Pharmakol, 1897 xxxix, 85
11 Kraft Arch d Pharm 1906 ccxliv 336
12 Barger and Carr Jour Chem Soc 1907 xci 337
13 Barger and Dale Jour Physiol 1909 xxxviii
14 Vahlen Arch f exper Path u Pharmakol 1908 lx 42
15 Cushny Jour Physiol 1906 xxxv 1

The two substances which seem to us to have the best claims to be regarded as the active principle of ergot are Jacobi's sphacelotoxin and hydro-ergotinin (ergotoxin) Barger and Dale strongly contest the claim of Jacobi that sphacelotoxin is a chemical individual They assert that the activity of this resinous body is due to contamination with the alkaloid ergotoxin (hydro-ergotinin), although Jacobi claimed to have isolated a small quantity of sphacelotoxin free from nitrogen, and physiologically active, the evidence brought forward to demonstrate the absence of nitrogen is not accepted by the English investigators, and we must

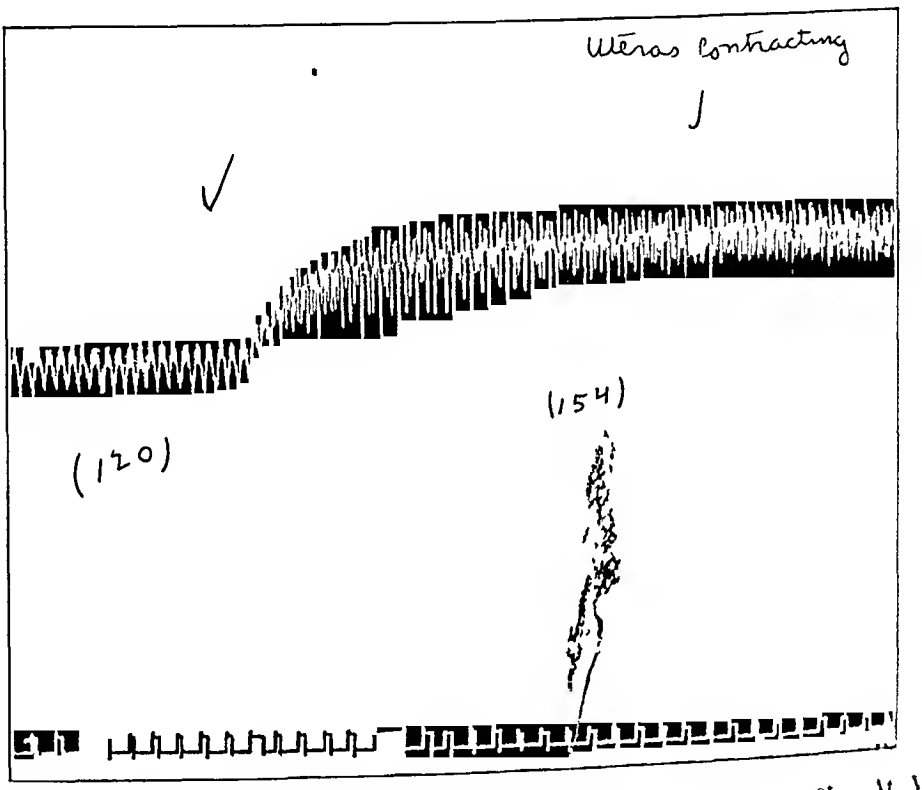

Fig 3 Showing activity of body extracted by benzol from ergot At V injection of 0 001 gm per kilo Time marker =5 seconds

confess that our views agree with those of Barger and Dale The quantity of nitrogen in sphacelotoxin according to our experiments is approximately 1 3 per cent and with the extremely small quantities of the principle with which Jacobi was working it is entirely possible that the nitrogen might have been overlooked

We have separated from ergot by means of benzol a body of great potency a dose of 0 0006 gm per kilo being sufficient to cause a distinct rise of blood-pressure On account of the large amount of fatty matter

in crude ergot, we have found it more advantageous first to extract with dilute alcohol, precipitate the resinous matter from this fluidextract with water and then to extract this precipitate with benzole The body which we have separated by this process is of an amber yellow color, soluble in acetone, ether, ethyl acetate, chloroform alcohol, benzol alkalies and strong mineral acids, insoluble in petroleum benzin, water or dilute acids If its alkalin solution be acidulated, a turbidity is produced but the precipitate is no longer soluble in benzol, showing that some chemical change has occurred during its union with the alkalies When boiled in a porcelain dish with sodium hydroxid, a cherry red color appears at the edge of the liquid With ferric chlorid, it yields, when fresh, a bright green color and, after keeping, a brownish color The solution in dilute alcohol when kept for a few days, becomes a grass-green color It contains about 1 3 per cent of nitrogen By prolonged shaking with acidulated water, it yields to the latter a substance which is precipitated by Mayer's reagent and the other alkaloidal precipitants If the extraction of a benzol solution of this body with a 1 per cent hydrochloric acid solution be continued until the aqueous shakings no longer respond to Mayer s reagent, the resin-like body that is left behind is physiologically inert and contains no nitrogen The nitrogenous body separated by this process represents about 9 per cent of the original substance and is extraordinarily active and responds to the usual tests for alkaloids

It seems to us improbable that the resin and alkaloid which compose this body are simply mixtures It will be remembered that Knebel[16] showed that caffein did not exist in kola-nut as free caffein, but in the form of a glucosid, to which he gave the name kolanin, which on decomposition yielded the alkaloid, glucose and an inert substance A similar state of affairs is the most plausible explanation of the close correspondence that we have found between the physiological activity of a specimen of ergot and the proportion of this body contained in it This fact will be considered in more detail later in the paper

Although the lack of definite statement by Jacobi as to the chemical properties of his sphacelotoxin, and his unfortunately indefinite use of the terms chrysotoxin and sphacelotoxin makes it impossible to assert positively the identity of sphacelotoxin and the substance we have separated by means of benzol yet the fact that the two have the same range of solubilities that they both turn green on standing and that their physiological powers are at least comparable in degree justifies us we believe in applying the term sphacelotoxin to this substance As regards

16 Knebel Die Bestandteile der Kolanuss Frankfurt 1892

the nitrogenous body which we have separated from our sphacelotoxin, we see no reason to doubt its identity with hydro-ergotinin (ergotoxin) In this connection it is interesting to note that in Dale's experiments, a dose of 1/3 mg per kilo in a cat produced a marked rise of blood-pressure with vasomotor reversal, while our alkaloid produced in a dog in a dose of 1/6 mg per kilo, a sustained rise of 34 mm

TABLE 2.—PROTOCOLS TO SHOW COMPARATIVE ACTIVITY OF PRINCIPLES SEPARATED FROM ERGOT

Time	Pressure	EXPERIMENT I
0	100	Inject 0 6 mg (per kilo) whole resin *
2	115	
4	124	
8	107	
Time	Pressure	EXPERIMENT II
		Pregnant bitch, abdomen opened to observe viscera
0	120	For past ten minutes no movements of uterus
1	120	Inject 1 0 mg (per kilo) of whole resin *
2	154	Marked contraction of circular fibers of uterus
3	150	Marked intestinal peristalsis
5	19	
10	9	Intestinal peristalsis more violent
Time	Pressure	EXPERIMENT III
0	110	Inject 0 16 mg (per kilo) of alkaloids *
5	145	
10	143	
17	140	
Time	Pressure	EXPERIMENT IV
0	88	Inject 0 2 mg (per kilo) washed resin *
1	80	
4	90	Inject 2 5 mg washed resin
6	96	

* For convenience, the body extracted from ergot by benzol is referred to as "whole resin" although it must be remembered that it is not all the resinous matter of the drug The term 'alkaloid" indicates the nitrogenous body separated from this resin and "washed resin' the inert material left after separating the alkaloid

BIOLOGICAL ASSAY

The first effort to standardize preparations of ergo by physiological means was made by Grunfeld [17] who used the method devised by Kobert based on the mortification of the comb and wattle of the rooster after large injections of this drug The method however was not generally used for several years until Houghton[18] published the results of some commercial applications in 1898 since which time it has been freely employed

17 Grunfeld Arb d Pharmakol Institut Dorpat 1895 xi xii, 295
18 Houghton Therap Gaz 1898 xiv 433

The theory of the cock's-comb test was that the ergot caused a violent contraction of the arteries, preventing the circulation in the comb and thus leading eventually to a dry gangrene although as at present applied the final reaction is only transient darkening in color There is, however, no convincing evidence that the interruption of the circulation is due to arterial spasm If it were, one would expect an ischemia rather than a congestion The fact that much larger doses are required to cause the bluing of the comb than are required to produce constitutional symptoms shows that the effect is a violent toxic one rather than a physiological one According to our experience, one-third of the quantity which is needed to cause the least perceptible change in the comb is sufficient to cause diarrhea, that is, to stimulate intestinal peristalsis in the chicken and if the relative susceptibility of the intestinal tract and the vasomotor system is the same as in the mammal, this dose would carry us into the toxic stage of circulatory depression Von Recklinghausen[19] has shown that the cause of the gangrene is the formation within the arteries of a hyaline plug, but Kobert argued that this thrombus is formed on account of the slowing of the blood stream during the vascular spasm This view, however, seems hardly tenable in the light of the experiments of Ellinger,[20] who produced similar changes in the cock's comb with cantharides and it seems to us that Ellinger's argument is reasonable that the formation of the thrombus is due to an irritant action on the intima

From a practical standpoint the fifty experiments on the rooster which we have made have convinced us that this method of assay is too inaccurate to be of utility In the first place, the individual susceptibility of different chickens is so great that the same animal must be used for comparative experiments with a standard preparation of the preparation to be tested If this is done it is evidently essential that the dose must not be large enough to cause permanent changes in the circulation of the comb but lesser degrees of congestion are so difficult of comparison that it is almost impossible to determine accurately the final reaction In certain roosters for some unknown reason, we found it impossible as have other experimenters, to produce any bluing at all of the comb or wattle In one chicken that we experimented on a dose of 2 1 c c of fluidextract of ergot gave rise to distinct constitutional symptoms consisting of diarrhea rapid breathing and excitement, the comb did not become bluish but seemed a little paler than normal Larger doses produced more marked constitutional symptoms and a more pronounced blanching of the comb but although we gave as high as 30 c c

[19] Von Recklinghausen Handbuch der allgemeinen Pathologie 1883 349
[20] Ellinger Arch f exper Path u Pharmakol 1908 lvii 437

of the same preparation, no darkening of the comb occurred It is of interest to note that two weeks after this last dose, the crop of the chicken separated as a dry, hard, blackish mass without suppuration Grunfeld, as well as later investigators, has mentioned this local mortifying effect at the point of introduction of the drug whether administered by the mouth or hypodermically The point we wish to bring out is that in two of three instances of local gangrene in our experiments, there was no gangrene of the comb or wattle

On account of the uncertainty of the cock's-comb reaction we have not attempted to make any comparative tests with this and other methods of assay Edmunds, however, experimented with a preparation which produced a typical reaction in the rooster but was inert when tested on the uterus

In 1908, Edmunds[21] published a method of assay based on the quantity of ergot required to produce contractions in the uterus of a cat We believe that with proper precaution this method would be capable of giving reliable results, but there are a number of factors which make it in our opinion, less desirable than the one we have to suggest There are three objections to this method which seem to us of practical importance In the first place, there is no distinct end-reaction to show how vigorous shall be the uterine contractions which will indicate the action of the drug, secondly, it has been proven that there is a distinct difference in the susceptibility of the multiparous and nulliparous uterus and finally it doubles the difficulty of obtaining test animals

We may mention one other method, which has been used by Dale in testing certain preparations from ergot The Dale method is based on the observation that after the injection of certain principles derived from ergot a dose of adrenalin causes a fall of blood-pressure instead of a rise this he calls the vasomotor reversal This vasomotor reversal is apparently not characteristic of ergot itself Crown and Henderson found, as did we that using the crude drug, the action was extremely uncertain It is therefore not available for standardizing ergot

We have used a method based upon the amount of elevation of the blood-pressure caused by the injection of a standard dose of ergot[22] The

21 Edmunds C W and Roth G B Physiologic Assay of Nitroglycerin Tablets Digitalis Tablets and Fluidextract of Ergot Jour Am Med Assn 1908, li 2130

22 Since writing this paper we have seen a brief article published in 1907 (Pharm Jour and Tr 1907 lxxv 157) of which we were previously unaware by W E Dixon containing the statement that he found the effect on blood pressure to be a satisfactory means of standardizing ergot but does not describe the details of the method employed This communication of Dixon's antedates our first paper on this subject more than three years

objection which has been raised against vasomotor tests of the drug on the ground that it is mere assumption to claim that a specimen active in regard to the circulation is equally so to the uterus, is, in the light of recent research, untenable As has been shown above the characteristic effect of ergot is a stimulation of all unstriped muscle tissue of the body and the changes in the circulation, in the intestines and in the uterus are but a part of one general action All of those substances which have been suggested by various writers as the active principle of ergot have produced stimulation of blood-vessel as well as uterus, with the exception of Vahlen's clavin, which there is strong reason to believe is not active From a scientific standpoint there is no choice between a uterine and circulatory test for the drug, the preference must be made on purely utilitarian lines, which is the simpler and which yields the most reliable results We shall consider the accuracy of results after description of our method

The first thought in estimating the strength of the drug through its effects upon the circulation would be to compare the effects of the specimen being tested with the effects of a standard preparation in the same animal as is done, for instance, with adrenalin This in the case of ergot, however, is impossible because the drug lingers for so long in the system We have already noted that the blood-pressure may remain high for at least two hours after the injection of a single dose, but even after the pressure has returned to the normal apparently there still remains some of the drug in the system, for we have found that the effects of a second dose of the same preparation cannot be compared to the effects of the first dose even if the pressure has returned to normal in the interval between the two injections In all the experiments quoted in this paper we have considered only the effects of first doses

Another method which would seem obvious, would be to ascertain the amount of drug necessary to produce a certain arbitrary rise in the blood-pressure in a series of animals Our early experiments were carried out with this idea but we were forced to abandon it because certain samples produced no rise at all, but especially because the amount of elevation did not vary according to the size of the dose A dose of 0 12 gm per kilo would produce as high a rise as double or treble or even four times this quantity This point we shall consider later but we will call attention here merely to Table 3 which shows the results of some of our early experiments bearing upon this fact

Having demonstrated that the degree of action bore no relation to the size of the dose we next carried out a series of experiments to determine whether the response was constant in different animals for the same dose

of the same preparation The idea was to adopt a standard dose and measure the activity of the preparation by the rise of blood-pressure which followed the injection of this quantity

TABLE 3.—EXPERIMENTS TO SHOW THAT EFFECTS DO NOT VARY WITH THE DOSE

Sample	Dose per kilo	Maximum rise in mm	Sample	Dose per kilo	Maximum rise in mm
P D No 1	0 10	35	H K M	0 12	6
	0 16	77		0 20	21
	0 36	32		0 32	27
P D No 2	0 13	25	Lilly	0 07	24
	0 24	20		0 24	12
	0 48	20		0 41	41
Squibb No 1	0 14	24			
	0 29	62			
	0 33	44			
	0 34	52			
	0 35	45			

After some twenty experiments, we came to the conclusion that although there was some general agreement in the amount of elevation of the pressure, it was not close enough to be satisfactory for quantitative work (see Tables 3 and 4) A close examination of our tracings however showed that in those instances in which the pressure had ascended abnormally high it was not so well sustained as in those in which the first rise had been less striking, in other words, there was a tendency for a closer correspondence some time after the injection of the drug than immediately after Our experience led us in a previous paper [2] to adopt empirically, ten minutes after the injection as the period yielding the most constant results Since the publication of this communication however further evidence has convinced us that it is necessary to take into consideration the total rise over the whole ten minutes so that at present our figure of physiological activity is obtained by using the primary rise which follows immediately after the injection and the elevation at five and ten minutes after the injection respectively and taking the average of the three figures which gives us approximately the average rise for ten minutes after the injection

TABLE 4.—SHOWING THE MAXIMUM RISE PRODUCED BY DOSES OF 0 33 C M PER KILO

P D No 2	Squibb No 1	S K F No 1
70 mm	47 mm	40 mm
27 mm	45 mm	50 mm
75 mm	50 mm	65 mm
57 mm	62 mm	
89 mm	55 mm	
57 mm	42 mm	

[2] Wood and Hofer Univ Penn Med Bull 1909 xxi 318

In Table 7 are the results of eighty-four tests of twenty-two samples of ergot It will be noted in this table, that in 55 per cent of the experiments, the average rise is within 5 mm of the average for the whole series with each preparation For instance, with preparation Squibb No 2, there are five tests, and of these, the average of the whole group being 36 6 mm the lowest rise was 28 and the highest was 42 while the other three were less than 4 mm from the total average of the series If we extend the limit of error to 10 mm departure from the average, only 20 per cent will be outside the limit It is evident, therefore, that where we have three closely agreeing results, the average of the series will almost certainly be within 5 mm of the theoretically correct figure for that specimen

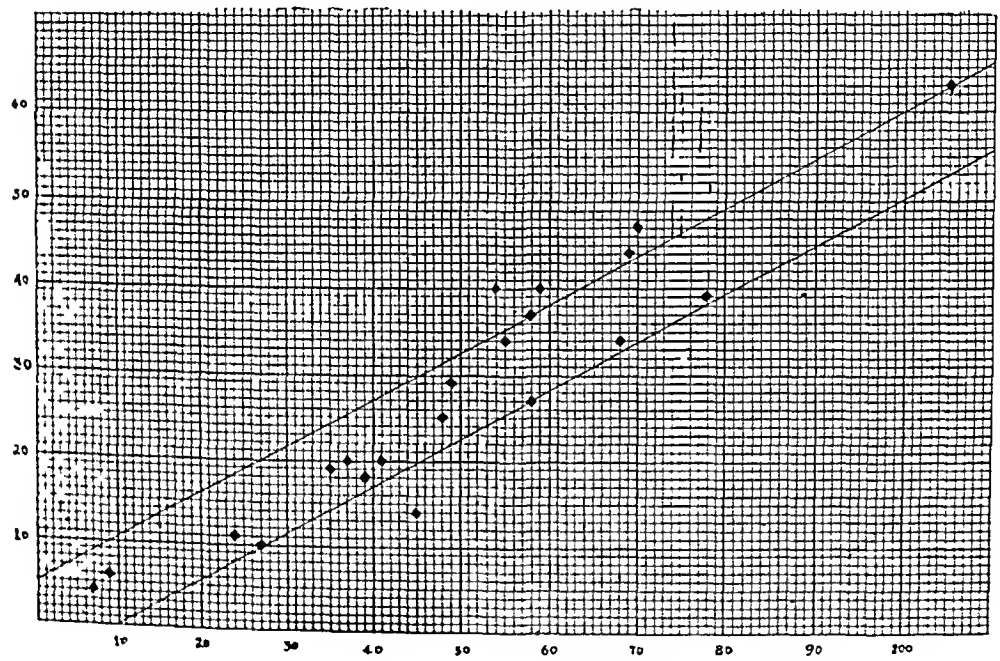

Fig 1 Results of comparative physiological and chemical assay of various samples of ergot Figures on abscissa = parts sphacelotoxin per 10,000 figures on ordinate = rise of blood-pressure in millimeters of mercury Oblique lines represent variations of 5 mm in the rise of pressure

One surprising fact is that the activity of the specimen bears no relation to the size of the dose which is required to produce the maximum rise for that sample the rise of pressure caused by any specimen of ergot is just as great after an eighth of a gram per kilo as after a fourth or even a half no matter whether we are dealing with an inert or highly active sample This is apparently so contrary to the accepted laws of pharmacology that we were very loath to believe it but our experience covering now some two hundred tests allows in our mind no doubt

The truth of this statement may readily be seen by referring to Table I For instance in preparation marked Squibb No 2 F we have doses ranging from 0 13 to 0 20 gm per kilo, the highest pressure in this instance being produced by the smallest dose In sample marked Retail No 1, the doses range from 0 13 to 0 25 and the effects in each instance are practically identical With retail sample No 2, although the dose in one instance was as high as 0 55 gm, we obtained practically no evidence of stimulation of the vasomotor system In a fluidextract which was made in our own laboratory, marked in the table Wood No 1 the effects of 0 16 gm were exactly the same as those of a dose of 0 24 gm

It therefore becomes necessary to determine the dose which will produce the best results in the majority of animals Of course there will

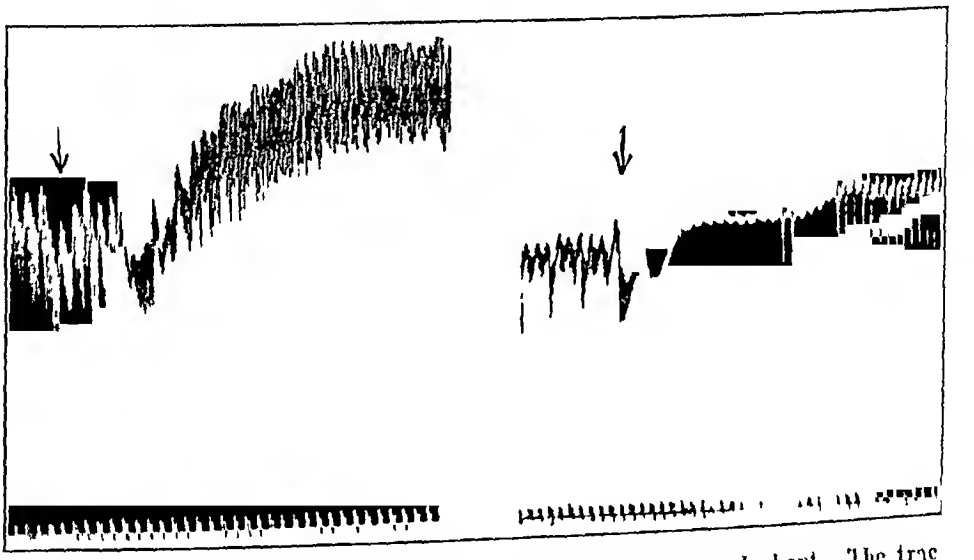

Fig 5 Showing the deterioration in ergot when improperly kept The tracing on the left shows the effect of a fluidextract of ergot which had been kept hermetically sealed the one to the right shows the effect of the same dose of the same preparation after being exposed to the air for 46 days

be more or less frequent individual variations in the susceptibility of dogs to ergot so that what is the full physiological dose for one dog may be too small for a second and toxic for a third, but this error can be avoided by a means which we shall mention later For the present we wish to determine the dose for the average animal this must be large enough so that in the majority of cases it will produce the greatest effect possible for that specimen of ergot, and small enough that it will not cause toxic effect in any considerable number of experiments As evidence of a toxic action we have taken the fall of pressure to a point

below normal within a period of ten to fifteen minutes after the intravenous injection of the drug

We have as available for determining the limit of probable toxicity, the results of 111 experiments which may be tabulated as in Table 5

TABLE 5—PER CENT OF TOXIC EFFECTS AFTER DOSES OF VARYING SIZES

	No experiments	Fall below normal Per cent
0 0 10 gm per kilo	2	0
10-15 gm per kilo	30	10 0
16-20 gm per kilo	49	16 3
21-25 gm per kilo	9	22 2
Above 25 gm per kilo	21	38 1

It will be seen that with doses ranging between 0 10 and 0 20 gm per kilo, we have toxic effects in about 13 per cent of the experiments and that above the latter limit, the toxic results occur in a much larger number of instances

To determine the low limit, that is, the smallest dose which is likely to produce the full physiological effect, we have compared the results of a second injection of the same dose at an interval of not less than ten minutes after the first injection If the blood-pressure is higher above the normal after the second dose than after the first dose, we consider that the full physiological action was not produced by the first dose We give a table covering the results of 52 experiments bearing upon this point In this table, it will be noted that with doses of less than 0 10 gm in every instance the blood-pressure was driven higher by a second dose, while with doses ranging between 0 10 and 0 20 gm in 88 per cent of cases the first dose produced full physiological action

It is evident from these two tables that, most generally, efficient doses of ergot will be equivalent to about 0 15 gm per kilo of body weight

TABLE 6—PER CENT OF INSTANCES IN WHICH SECOND DOSE CAUSED A RISE TO A POINT HIGHER THAN THAT PRODUCED BY FIRST DOSE

	No of experiments	Higher after second dose
0 10 gm per kilo	4	100 0 %
11-15 gm per kilo	19	26 3 %
16 20 gm per kilo	9	12 5 %
Above 20 per kilo	20	5 0 %

DESCRIPTION OF METHOD

Our method as finally worked out is as follows A dog is given hypodermically from 0 02 to 0 06 gm morphin sulphate according to its size and after the morphin has had time to act, is tied down and lightly etherized The carotid artery is connected with a mercury manometer

and the jugular vein prepared for injection The animal is then allowed to recover from the ether, the blood-pressure not being considered normal until it has remained at a constant level for at least ten minutes after withdrawing the anesthetic A dose of the preparation under question is then injected, equivalent to approximately 0 15 gm of ergot per kilo and the pressure observed for fifteen minutes At the end of that time a second dose should be administered in order to ascertain that the full effects have been brought out by the first injection After watching the effects of the second dose for ten minutes the dog is killed usually by injecting chloroform into the vein

To obtain the results which we have described above, there are certain sources of error which experience has taught us must be sedulously avoided Foremost among these, we wish to emphasize the necessity of the completeness of the recovery from the anesthetic before the administration of the drug Not only are there likely to be changes in the blood-pressure during the convalescence from anesthesia so that it is impossible to establish the norm accurately but we have found as have also Cronyn and Henderson, that the effects of ergot are very frequently atypical if any large quantity of ether is still circulating in the system (Whether Henderson's anesthesia by intracerebral injection of magnesium chlorid would be available for this purpose we cannot say positively but would think it *a priori*, improbable) In order to avoid fallacies from ether, we advise that the anesthesia be as light as compatible with prevention of suffering during the operation, and that the blood-pressure be observed at intervals until it has remained at the same level for ten minutes before injecting any ergot

While, of course the perceptive centers of the dog are much benumbed by the morphin, we have found that in many cases there is a marked circulatory response to psychical influences as shown by alterations in the blood-pressure from whistling or calling For this reason, complete silence especially the avoidance of conversation and sudden noises during the experiment is essential

Our results in summer indicate strongly that when the room temperature is too high the results are not altogether trustworthy Into this question we have not gone in detail but would not have much confidence in assays made in a room with a temperature of more than 25 C (77 F)

Several other factors which are usually believed to have an influence on the effects of drugs deserve a word or two of mention Age appears to be a factor only in so far that immature animals are more susceptible to the drug so that toxic effects are almost the rule with pups We could observe no difference from sex The sizes of our dogs have ranged from

1 to 20 kg in weight, but with doses proportional to weight, we could see no distinction The breeds were of all kinds, with a large preponderance of mongrel, the ordinary street dogs of a large city

TABLE 7 —RESULTS OF 84 TESTS OF 22 SAMPLES OF ERGOT

Preparation	Dose	Primary rise	5 Min rise	10 Min rise	Average rise	
Squibb No 1	33	47	32	2	27	
	34	50	33	8	30	
	35	45	33	9	29	
Average	34	47 3	32 7	6 3	28 7	
Squibb No 2	0 05	10	5	4	6	Fresh
	0 13	56	30	30	42	
	0 15	50		30	40	
	0 16	55	40	25	40	
	0 16	40		25	33	
	0 26	35	25	25	28	
Average	0 172	47 2	34 7	27	36 6	
Squibb No 2	0 16	40		25	33	Sealed bottle two months old
	0 17	64	50	35	53	
	0 18	clot	32	17	32	
	0 18	50		15	32	
	0 18	34	34	25	31	
	?	75		25	50	
	0 18	90		10	50	
Average	0 175	58 8	41 7	21 7	40 5	
Squibb No 2	0 15	15		0	7	Open bottle two months old
	0 17	51		11	31	
	0 19	20	21	15	19	
	0 33	32	23	6	20	
Average	0 21	29 5	22	8	19 5	
Squibb No 3	0 13	46		27	36	Fresh
	0 16	45		30	37	
Average	0 145	45 5		28 5	37 0	
Squibb No 3	0 13	42	25	5	24	Sealed bottle four months old
	0 16	34	31	23	29	
	0 16	26	27	25	26	
	0 17	43	28	18	30	
	0 18	43	36	29	36	
Average	0 16	37 6	29 4	20	29	
Squibb No 4	0 13	70	25	12	36	Sealed
	0 14	69	69	60	66	
	0 15	48	46	49	48	
	0 15	49	41	15	35	
	?	59	54	43	52	
Average	0 143	59	47	35 8	47 4	

TABLE 7—Continued

Squibb No 5	0 13	48	33	26	36	
	0 15	79	16	25	40	
	0 18	45	51	35	44	
Average	0 153	57 3	33 3	28 7	40	
Retail No 1	0 13	23	20	7	17	
	0 22	35	10	8	18	
	0 25	28	27	9	19	
Average	0 175	29	19	7 5	18	
Retail No 2	0 13	10	0	0	3	
	0 40	10	5	0	5	
	0 55	15	5	0	7	
Average	0 36	11 7	3	0	5	
S K F No 1	0 14	31	30	28	30	Fresh
	0 33	50	48	35	44	
	0 33	65	65	49	60	
	0 51	65	60	40	55	
Average	0 328	52 8	50 8	38	47 3	
S K F No 1	0 16	36	22	16	25	Kept corked
	0 19	22	11	10	14	
	0 19	26		15	20	
	0 29	22	15	12	16	
Average	0 208	26 5	16	13 3	18 8	
S K F No 1	0 21	42	14	20	25	Sealed bottle
	0 22	30	24	20	25	
	?	42	31	20	31	
	?	32	11	10	18	
Average	0 215	36 5	20	17 5	24 8	
S K F No 2	0 10	33		6	19	Sealed bottle five
	0 14	48	43	34	42	months old
	0 16	44	42	21	36	
	0 16	53	36	8	32	
	0 16	58	46	29	44	
Average	0 155	50 8	41 8	23	38 5	
S K F No 2	0 16	30	13	11	18	Open bottle four
	0 16	12	6	clot		months old
Average	0 16	21	9 5	11	13 8	
S K F No 2	0 19	28	27	24	26	Open bottle one
	?	34	30	?	23	month old
Average	0 19	31	28 5	13 5	24 3	

TABLE 7—Continued

Cook No 1	0 14	34	27	18	26	Fresh
	0 14	44		24	34	
	0 14	30		15	22	
	0 16	86		66	76	
	0 21	15		6	11	
Average	0 158	41 8	27	25 8	33 8	
Cook No 1	0 15	38	34	18	30	Sealed bottle one
	0 16	84	74	53	70	month old
	0 17	63		31	47	
Average	0 16	61 7	54	32 7	49 0	
Cook No 1	0 12	30	35	38	34	
	0 13	40	39	27	35	
	0 13	52	22	22	32	
Average	0 127	40 7	32	29	33 7	
Cook No 2	0 17	37	17	7	20	
	0 18	15	9	6	10	
	0 17	7	2	0	3	
Average	0 175	19 7	9 3	4 3	11 0	
Wood No 1	0 16	46	35	22	34	
	0 17	40		13	27	
	0 24	45	30	25	33	
Average	0 19	43 7	32 5	20	31 3	
Special	0 14	15	4	2	7	
	0 14	12		0	6	
	0 20	36	20	16	24	
	0 23	37	34	22	31	
	?	30	25	18	26	
Average	0 178	26	20 8	11 6	18 8	

CHEMICAL ASSAY

The only methods employed for the chemical assay of ergot have been various modifications of that of Keller, which is based on the percentage of total alkaloids present As far as our reading goes, there is no experimental evidence to show that the figures obtained by Keller's method of assay bear any relation to the physiological activity of different specimens of ergot The paper of Dohme and Crawford which is sometimes quoted as demonstrating the value of Keller's test, is open to several serious objections It really proves nothing beyond the fact that one can obtain from ergot physiologically active alkaloids Vanderkleed found that the relationship between the percentage of alkaloids and the activity of ergot when tested by the cock's-comb method is extremely

precarious It has been pointed out by Barger that the fallacy of Keller's method resides chiefly in the fact that the alkaloids extracted consist of a mixture of the active hydro-ergotinin and the inert ergotinin, and that as there is no method of separating these alkaloids, the resultant figures are untrustworthy

In the course of our experiments in the biological standardization of ergot, we were struck by the fact that those samples of fluidextract which gave but little precipitate on the addition of water were uniformly of low potency, this led us to investigate the possible relation between the percentage of resinous matters and the activity of the drug After experimenting with various solvents, we finally decided on the following method Take 10 c c of fluidextract of ergot, add 20 c c of water shake with repeated portions of 10 c c each of benzol, until the latter comes away colorless, unite the various portions of benzol in a tared dish evaporate over a water bath and dry at a temperature of 37 C to constant weight We may remark in passing that almost uniformly very troublesome emulsions are formed, these can be most readily broken up by the method suggested by Dunn, of adding filter paper to the emulsion

We have already described the chemical nature and physiological properties of the body which is obtained by benzol extraction We wish at this place, simply to emphasize the fact that the benzol extractive does not represent the total resin of ergot, the proportion of the water-insoluble substances which are dissolved by the benzol varies greatly in different specimens

Whether or not our ideas of the nature of this substance are correct we are well satisfied that the amount present is an accurate indicator of the activity of the fluidextract of ergot We give herewith (Table 8) the results of comparative physiological and chemical assays of twenty-one samples of fluidextract,[24] ranging in physiological activity from 4 to 63, covering the whole gamut of possible degrees of power It will be noted that the percentage of benzol extractive increases regularly as the physiological activity becomes greater There are, as might be expected, one or two slight deviations from mathematical exactitude but these are mostly well within the limit of error In the case of the sample marked Special, two of the physiological tests differed very widely from the rest of the series (see Table 8) Excluding those two experiments the physiological figure would be 27 instead of 19

24 The sample labeled Wood No 2 is a 50 per cent tincture, but is calculated to correspond to fluidextract strength

TABLE 8—RESULTS OF COMPARATIVE PHYSIOLOGICAL AND CHEMICAL ASSAYS OF 21 SAMPLES OF ERGOT

Preparation	Per cent of Sphacelotoxin	Rise of Blood pressure
Sq Exp	0 07	4
Warner	0 09	6
Retail No 4	0 27	10
Cook No 2	0 24	11
S K F No 1 (C)	0 35	19
Squibb No 2 (O)	0 37	20
Cook No 1 (O)	0 39	18
Wood No 2	0 42	20
S K F No 2 (O)	0 45	14
S K F No 1 (S)	0 48	25
Squibb No 3 (S)	0 49	29
Cook No 1 (S)	0 55	34
Squibb No 5	0 54	40
Special	0 58	19
Squibb No 3 (F)	0 58	37
Squibb No 2 (S)	0 59	40
Cook No 1 (F)	0 68	34
Squibb No 4 (C)	0 69	44
Squibb No 4 (S)	0 70	47
S K F No 2 (S)	0 78	39
S K F No 2(F)	1 05	63

For easier comprehension of these results, we have plotted them in a diagrammatic form, in Figure 4, the abscissa represents parts per ten thousand of sphacelotoxin and the ordinate millimeters of rise of blood-pressure We have drawn on this figure, two parallel lines representing variations of 5 mm in the blood-pressure above or below the average which is the limit of accuracy we claim for our method of physiological assay In this figure, four specimens are slightly outside of these limits Of these, one is the sample labeled in our Table S K F No 2 (O), of this sample unfortunately, we have but two physiological tests and one of these is not complete on account of a clot at the end of the ten minutes, so that we can place comparatively little reliance on the physiological figure Of the other four samples which fall without the limits mentioned only one is more than 3 mm of pressure outside these limits, so we feel justified in claiming that there is a marked degree of parallelism between the physiological activity of the drug and the percentage of sphacelotoxin

Another fact which is strongly corroborative of the value of this method of assay is that in specimens which have deteriorated from long keeping, the diminution in the amount of sphacelotoxin runs closely parallel to the loss of physiological power (see Table 12) Thus S K F No 2 when fresh gave a chemical assay of a little over 1 per cent and caused a rise of blood-pressure of 63 mm A sample of this fluid

extract kept hermetically sealed, showed six months later a sphacelotoxin content of 0 81 per cent , the same preparation, left uncorked, fell in its chemical assay from 1 05 to 0 45, and in its physiological figures from 55 to 13 Similar parallelism may be noted in the case of Squibb No 4 Squibb No 3 and Cook No 1

A further confirmation of our beliefs we are enabled to offer through the courtesy of E R Squibb and Son This firm prepared for us two concentrated preparations from the same sample of crude ergot, one of which contained 0 5 per cent of alkaloid by Keller's method and 0 7 per cent of sphacelotoxin, the other preparation contained the same amount of alkaloid but yielded 4 0 per cent of sphacelotoxin The former preparation, rich in alkaloid, when injected into the dog in doses of 22 mg per kilo caused a rise of 14 mm in the blood-pressure, and in a dose of 53 mg gave a rise of but 24 mm The other preparation, which contained a high percentage of resin, gave in doses of 23 and 29 mg, 40 and 45 mm rise respectively

TABLE 9.—COMPARISON OF TWO PREPARATIONS FROM THE SAME SAMPLE OF ERGOT

Preparation	Per cent alkaloids	Per cent sphacelotoxin	Dose gm	Rise of pressure
A	0 55	0 70	0 022	13
			0 053	24
B	0 60	4 04	0 023	34
			0 029	41

Further evidence of the value of this method of assay is derived from a study of the comparative activity of the matter extracted by benzol and the residue left behind after benzol extraction In Table 10 are the protocols of three experiments made with different portions from fluidextract Cook No 1 It will be seen, that while large doses of the watery residue produced a slight rise of the blood-pressure, the effect was in no way comparable to the strength of the whole fluidextract Thus in Experiment 2, the injection of an amount of the marc of the fluidextract equivalent to 0 12 gm of the original fluidextract produced a rise of 10 mm , 0 15 gm more of the same preparations produced a maximum rise of 29 mm above the normal (we did not wait long enough to determine how well this rise would be maintained), but an injection of the benzol extract from the same preparation representing 0 15 gm of ergot produced a maximum rise of 55 mm above the normal, or 26 mm above the point at which the injection was made

The activity of a number of these watery residues in comparison with the activity of the whole fluidextract is presented in Table 11

TABLE 10—ACTIVITY OF WATERY RESIDUES IN COMPARISON WITH THAT OF BENZOL EXTRACT

Time	Pressure.	
Fluidext Cook No 1		
0	97	Inject watery residue equivalent to 0 15 gm fluidextract
1	105	
4	97	
15	100	Inject 0 15 gm more of watery residue
16	108	
19	100	Inject benzol extract equivalent to 0 21 gm fluidextract
22	123	
28	119	
35	128	
Cook No 1		
0	95	Inject 0 12 gm watery part
2	105	
4	105	Inject 0 15 gm more (watery part)
8	124	
9		Inject 0 15 gm benzol soluble
10	150	
12	145	
Cook No 1		
0	114	Inject benzol extract—0 28 gm ergot
2	142	
5	140	
6		Inject benzol extract—0 11 gm ergot
8	142	
12	145	
13		Inject watery residue—0 17 gm ergot
15	153	
17	145	
19	140	

TABLE 11—ACTIVITY OF WATERY RESIDUES IN COMPARISON WITH THAT OF FLUID EXTRACT

Sample	Part used	Dose	Max rise	Av rise
Squibb No 3	Fluidextract *	0 15	45	37
Squibb No 3	Watery residue	0 17	25	12
Squibb No 5	Fluidextract*	0 15	57	40
Squibb No 5	Watery residue	0 17	4	1
Squibb No 5	Watery residue	0 23	10	7
Cook No 1	Fluidextract *	0 16	42	34
	Watery residue	0 15	8	4

* Averages from Table 7

The possession of a slight degree of activity by the residue is not in our opinion, a potent objection to the method The United States Pharmacopeia recommends the assay of opium for its morphin, neglecting other active alkaloids which are present and it must certainly be true that the residue left behind in the opium after extraction of the morphin is not entirely inert in the same way, nux vomica is assayed for its strychnin, entirely overlooking the presence of brucin It is apparent therefore that chemical assay may be satisfactory even if a slight degree of potency remains in the marc

We have met, however, with a more serious objection to our method of chemical assay in testing preparations other than the fluidextract For instance, Squibb sent us an experimental preparation of ergot which showed 0 45 per cent of Keller cornutin and 0 21 per cent of sphacelotoxin This percentage of sphacelotoxin corresponds to physiological activity of about 10, yet a dose of 0 16 c c of this sample produced a rise of 53 mm It is evident, therefore, that it is possible to obtain a watery solution of ergot which contains so large an amount of parahydroxyphenylethylamin, or some other principle, as to produce a considerable rise in the blood-pressure although the sphacelotoxin content may be very low, but also it is possible to obtain a preparation from opium, almost free from morphin, which would be highly depressant to the respiratory center through a large amount of codein We would point out that while it may be possible to make watery preparations of ergot which will give, when tested by the blood-pressure method, high figures yet such preparations are made at a great waste of ergot For instance, the preparation just mentioned was supposed to be four times the strength of the fluidextract, and yet when tested physiologically it was in the same class with an active fluidextract In other words, there had been a loss of ergot amounting to 70 per cent We have found that all those watery preparations which we have examined have been far below the strength which the manufacturers claimed for them

Another exception to our assay method is in the case of preparations made with glycerin, as for instance, by the formula suggested by G M Beringer [25] We have examined two such preparations, one made by Mr Beringer himself and the other by Professor Cook One of these gave a physiological figure of 21 but yielded only 0 19 per cent of sphacelotoxin The other gave a rise in blood-pressure of 15 mm but only 0 08 per cent of benzol extractive

CAUSES OF THE POOR QUALITY OF ERGOT

There has long been great dissatisfaction among clinicians with the quality of ergot which is available for practical use Our investigations show that this distrust is well grounded Of four preparations which we have obtained from the most reputable retailers in Philadelphia, the most active gave an average sustained rise of only 18 mm the other three gave respectively 10 11 and 5 mm If this is what may be expected from the better class of retail pharmacists it is apparent that the fluidextract of ergot as ordinarily dispensed on prescriptions is nearly inert

25 Beringer Proc Am Pharm Assn 1908 lvi 981

There are four possible causes for the lack of activity of commercial samples of preparations of ergot (1) original meritness of the drug (2) changes taking place in the crude drug, (3) improper methods of extraction, (4) changes taking place in the preparations after manufacture We shall consider these four causes seriatim, and endeavor to find out the most important ones and to point out a remedy for the present undesirable condition

As to differences in the activity of a fresh drug owing to possible influences of climate, soil, and so forth, our evidence is comparatively meager It is so difficult to obtain authentic samples of the crude drug from different localities that it is almost impossible for investigators to accurately determine this point Our sole evidence is based upon three samples of ergot Through the courtesy of H K Mulford and Company, we were provided with a sample of German ergot and one of Spanish ergot We found the Spanish more active than the German ergot

As to the deterioration which takes place in crude ergot, this may be the result of one of two causes, the attacks of insects to which the drug is peculiarly liable, or spontaneous chemical changes taking place in the drug Grunfeld tested a sample of crude ergot by the cock's-comb method at varying intervals He found it required, in October, twice the dose that it did in August to produce the same degree of reaction and that in February it required eight times this dose, in April twelve times the dose, and by the following June no dose would produce the reaction This would indicate a deterioration in the first two months of keeping, at the rate of 6 2 per cent a week, in the first six months of keeping a rate of 3 5 per cent per week, and in nine months of keeping a rate of 2 8 per cent a week We attempted to make an investigation into this point, but owing to various obstacles, the results are of no value

Grunfeld does not mention how the ergot was kept, except that it was powdered Although the experiments which we made as regards the keeping quality of crude ergot do not throw any light on the rate of deterioration they are at least suggestive as to the influences of different methods of storing On November 1, 1908 we received from Smith Kline and French a sample of fluidextract (marked in our tables as S K F No 1) and also a sample of the ground ergot from which this fluidextract was made The ground ergot was divided into three portions one of which was kept in a paper box the second hermetically sealed in a glass bottle and the third was dried for forty-eight hours at a temperature of 37 C and then hermetically sealed At the time this ergot was received we had not yet worked out our method for a chemical assay of the drug and the figures on this point are therefore lacking

The physiological test which was made of this fluidextract at the time it was received showed a rise of 47 mm, but this figure is evidently too low, when taken in the light of the chemical studies later made of the ground ergot The three samples of crude ergot were made up into fluidextracts by Professor Cook six months later and yielded the following percentages of sphacelotoxin

Sealed, 0 81

Dried and sealed, 1 10

Kept in paper box, 0 93

These figures indicate that the best method of keeping crude ergot is to dry it at low temperatures and then to protect it from atmospheric influences by keeping it hermetically sealed

If crude ergot loses strength as rapidly as the figures of Grunfeld indicate, it is evidently important to determine the length of time which ordinarily elapses between the harvesting of the ergot and its manufacture into fluidextracts In the present condition of the ergot business, both in Europe and in this country, it is almost impossible to know definitely the age of any individual sample of ergot Some of the larger manufacturers have their own agents in the ergot districts of Europe, and are therefore able to know within reasonable probability of the freshness of their supply, but the smaller manufacturers who have to rely on general importers of the drug are entirely at the mercy, first, of the European dealers, who will hold over from year to year any of the drug not sold immediately after its collection, and also of the jobbers in this country who sell, of course, any stock that they happen to have on hand We have a sample of ergot, obtained from a London exporter by H K Mulford & Co, which was received in London in 1904 with the statement that it had been kept in cold storage for three years, and when it reached our hands in 1908 was therefore at least seven years old It was thoroughly worm-eaten, but in its general appearance vaguely suggested ergot In the letter which accompanied it, was the naive statement by the exporter that "if sifted, it would look presentable, but could be salable at current prices only if a scarcity came along or if wanted for a cutting contract for some institution"

As bearing on the quality of ergot which is made up into fluidextracts, it is interesting to note that of seven fluidextracts which were furnished us directly by the manufacturer, six reached a reasonable standard of activity one specimen was practically inert

Some years ago, Dr E H Squibb had a fluidextract of ergot prepared by his firm, carried by a ship surgeon on a voyage around the world and when, in the course of time it came back to him, he tested it

chmically and came to the conclusion that it was active A similar observation to that of Dr Squibb has been reported by Sharp[26] with a liquidextract of the British Pharmacopeia, which he found active after twelve months Largely on the basis of Dr Squibb's observation the belief is prevalent among pharmacists that the fluidextract of ergot is a stable preparation, and that the cause of the poor quality of the drug on the market is owing to changes in crude ergot before manufacture

We would point out, however, that such evidence is practically worthless In the first place, there was no definite knowledge of how active the preparation of ergot was when manufactured and in the second place, no reliable information as to the activity at the end of the year Chmical tests cannot be considered as scientific evidence in such questions

We have, moreover, very convincing proof that the fluidextract of ergot is fully as unstable, if not more so, than the crude drug The evidence of this, as well as of some points which bear upon the causes of this change, are summarized in Table 12 In this table, the samples S K F No 1 and Squibb No 2, were received from the manufacturers before the chemical method of assay was worked out and for purposes of accuracy in relative strengths we have much more confidence in our chemical assay than in any physiological test The figures which are given for these two samples for the percentage of sphacelotoxin represent the theoretical per cent that a preparation giving the corresponding physiological figures should contain

The method of studying the rate of change which took place was as follows As each new sample of fluidextract was received it was divided into three portions one of which was hermetically sealed in a bottle from which practically all the air had been excluded, the second was put away in a bottle simply stoppered with cotton to keep out the dust thus permitting free exposure to the air the third bottle was used for immediate tests This third portion was opened from time to time to take out small quantities such as were needed, imitating closely therefore the conditions under which it would ordinarily remain on the pharmacist's shelf

It will be noted that in the bottle exposed to the air, the loss of potency was comparatively rapid in one case as high as 5 5 per cent each week, and in every instance the preparation had lost at least 50 per cent of its active principle within a period of five months On the other hand, those samples which were kept hermetically sealed lost their strength much more slowly the most rapid of these according to the

[26] Sharp Merck's Rep November 1908 p 302

table, being that of S K F No 1, which deteriorated at the rate of 2 3 per cent a week This figure, however, is hardly fair, because the sample had been kept in a bottle which was opened at various intervals for some two weeks before it was sealed, at the time of sealing this bottle the fluidextract gave, in two experiments which were made at that time, a physiological activity of only 20, so that it is probable that change had already taken place in the preparation before it was removed from atmospheric influence Leaving out this sample we find that the diminution in sphacelotoxin content ranged from 0 2 to 1 1 per cent a week In the cases of those bottles which were corked, but from which the air was not entirely excluded, the loss of potency was, as might be expected midway between the sealed and the open bottles, showing an average of about 2 6 per cent a week

Another preparation made for us by Professor Cook may be quoted although owing to an unexpected pharmaceutical problem the evidence is somewhat complicated Professor Cook sent us, in May a fluidextract made according to the United States Pharmacopeia of 1880 and divided into two portions, one of which had been filtered after percolation, the other not A portion of the unfiltered half, which contained 0 49 per cent of sphacelotoxin, was sealed, the filtered portion which gave 0 31 per cent was placed in an unstoppered bottle Four months later, the sealed (unfiltered) gave 0 45 per cent compared to 0 49 per cent when fresh the open bottle but 0 19 per cent compared to 0 34 per cent when fresh It is interesting to note also that a bottle of the unfiltered sample which had been kept corked but not hermetically sealed, gave at the same date 0 24 per cent of benzol extractive

TABLE 12—TEST OF FLUIDEXTRACT OF ERGOT (COOK NO 2) UNDER VARIOUS CONDITIONS OF FRESHNESS AND EXPOSURE

	Filtered	Unfiltered	
Fresh	0 34%	0 49%	
Sealed		0 43%	21 weeks old
Corked	0 24%	0 37%	21 weeks old
Open	0 18%		21 weeks old

The evidence quoted above as to the changes which take place in the fluidextract of ergot throw much light on the causes of the poor quality of drug which is found in the retail market In our opinion the inertness of a retail fluidextract of ergot is due chiefly to the length of time elapsing between the manufacture of the fluidextract and its sale to the patient Manufacturers are in the habit of storing away their fluidextract for varying periods of from three to nine months in order to allow it to settle and become clarified It then goes to the jobber who

may store it for another six months or a year It reaches the pharmacist at least one, and generally two years old, and stays on his shelf perhaps another year or two before it is dispensed to the patient While a tightly corked bottle is almost hermetically closed, so that the fluidextract as stored by the manufacturer is protected against the deleterious influence of the atmosphere, it must nevertheless be remembered that the loss of strength, even in sealed bottles amounts to nearly 50 per cent a year on the average It is evident, therefore, that it cannot be expected that a sample of fluidextract of ergot which has been kept for two or three years, even under the most favorable conditions, can possess a great deal of physiological power

One other factor of importance from a pharmaceutical standpoint deserves mention, and that is the means which are used for extracting the activities from the drug If our belief is correct that the most active ingredient of ergot is sphacelotoxin it is evident that no watery preparations of ergot can thoroughly represent the drug It is, of course conceivably possible that by an elaborate process of manufacture, the sphacelotoxin could be decomposed and the alkaloid hydro-ergotinin obtained This alkaloid, however, is itself almost insoluble in water, and according to Barger and Carr, the salts which it forms with the inorganic acids are likewise but slightly soluble so that even by extracting the alkaloid in the free state, we can hardly hope to obtain a highly active preparation of ergot Our experiments with various watery preparations of the drug bear out this deduction We have tested physiologically three samples of this class of preparations, two of which are on the market and recommended for hypodermic administration, the third being an experimental product which was sent us by the manufacturer who was attempting to obtain an active watery preparation of ergot Not one of these three samples equaled the figures which were claimed for them by the maker Two of them were almost absolutely inert and the third the label of which bore the statement that 1 c c equaled 4 gm of ergot was of about the strength of an ordinary fluidextract

Our conclusions as regards the quality of ergot which is at the disposal of the physician may be summed up as follows

1 Preparations of ergot obtained from retail pharmacists are almost universally far below the standard

2 No preparation of ergot which does not contain considerable amounts of alcohol or some similar inorganic solvent can thoroughly represent the drug

3 Starting with an active specimen of crude drug, a fluidextract freshly made, according to the process of the eighth revision of the United States Pharmacopeia, will furnish a potent preparation

4 Both the crude drug and fluidextract deteriorate comparatively rapidly

5 We would recommend, therefore, that all preparations of ergot should bear on the label the date of their manufacture, or at least the date beyond which the strength of the specimen cannot be trusted, as do the antitoxic serums, and should be preserved in small bottles, hermetically closed

TABLE 13.—LOSS OF STRENGTH OF ERGOT BY KEEPING

How kept	Physiological Test	Sphacelotoxin	How long kept wks	Loss per week %
	S K F No 1			
Fresh	47	70*		
Sealed	25	0 48	14	2 3
Corked	19	0 35	14	3 6
	S K F No 2			
Fresh	63	1 05		
Sealed	39	0 78	22	1 1
Corked		0 73	22	1 4
Open	14	0 45	20	2 8
	Squibb No 2			
Fresh	37	0 60*		
Sealed	40	0 59	7	0 2
Corked		0 45	25	1 0
Opened	19	0 37	7	5 4
	Cook No 1			
Fresh	34	0 70		
Sealed	49		5	
Sealed	34	0 55	22	1 0
Open	18	0 39	6	7 4
	Cook No 3			
Fresh	0 93			2 8
Corked	0 80		5	3 2
Corked	0 54		13	
	Cook No 4			
Fresh	1 10			2 4
Corked	0 75		13	
	Squibb No 4			
Fresh	0 95			2 3
Corked	0 69		12	2 2
Sealed	0 70		12	
	Experimental			
Fresh	4 04			1 7
Corked	3 12		15	

* Estimated from the physiological figure

SUMMARY

The important facts brought out in this paper may be summarized as follows

1 Ergot is a stimulant to all the unstriped muscle tissue of the body

2 As a part of this general action there is a stimulant effect on the arterial muscles and probably also on the heart

3 The action on the blood-vessels occurs after destruction of the vasomotor center and must be, therefore, the result of an effect on some portion of the peripheral vasomotor mechanism

4 The degree of elevation of blood-pressure affords an accurate criterion of the activity of ergot and is, in our opinion, the most available method for the biological assay of the drug

5 The active principle of ergot is an alkaloidal substance which occurs in the drug probably in chemical union with a resinous body For the combination we suggest the retention of the name suggested by Jacobi of sphacelotoxin and for the alkaloidal substance the term applied by Kraft of hydro-ergotinin

6 The percentage of sphacelotoxin varies accurately with the physiological activity of different specimens of ergot

7 The percentage of sphacelotoxin in a fluidextract may be easily estimated by precipitating with water and extracting with benzol

8 A fluidextract of ergot exposed to the air deteriorates extremely rapidly

9 The deterioration of fluidextract of ergot may be much retarded by protecting it against contact with the air, but under the most favorable conditions there is a loss of strength approximating 10 per cent a month

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THE UTILIZATION OF MILK-FAT BY AN ATROPHIC INFANT *

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This paper furnishes a comparison of the results obtained from three observations made on an atrophic infant in which the absorption of fat was determined Each observation lasted for three days, during which time the fat in the food and feces was determined

For twelve days immediately preceding the first observation the infant was fed exclusively on human milk and the first observation succeeded this preliminary period without interruption There was an interval of four days between the first and second observations and an interval of three days between the second and third observations

During the first observation the infant was given 840 c c of breast-milk daily During the second observation he was given 840 c c daily of a mixture of cows' milk containing approximately 3 per cent of fat, 6 per cent of milk-sugar and 1 per cent of protein

During the third observation the infant was given 840 c c daily of a mixture of cows' milk prepared with rennet in which the percentages of fat sugar and protein were approximately the same as during the second observation

In the interval between the first and second observations the infant was fed on breast-milk The reason for this will be referred to later In the interval between the second and third observations he was given the same preparation of cows' milk treated with rennet that he received during the third observation

Carmin was given at the beginning and end of each observation

PREPARATION OF THE FOOD

The fat in the cream that was used to prepare the cows-milk mixtures was determined each day by the Babcock method and the milk mixtures were prepared to contain approximately the desired percentage of fat In each feeding-bottle 105 c c of the mixture were put and to avoid any chance of accidental spilling the rubber nipples were fastened to the feeding bottles by strips of adhesive plaster The infant received eight

* From the Biochemical Laboratory of the Harvard Medical School

feedings in twenty-four hours After each feeding the bottles were set aside until the next day, and then they were carefully rinsed and the fat in the rinsings was ultimately determined and the amount deducted from the total fat ingested The amount of fat thus left was between 2 5 and 3 per cent of the total quantity ingested

In the third observation rennet was added to the milk to produce a finer subdivision of the fat It appeared probable that, when cows' milk coagulated in more or less large and tough curds in the stomach, some of the fat which was enmeshed in these curds escaped digestion If, therefore, the casein was coagulated before ingestion and was then passed through a fine-meshed sieve it was hoped that, though the fat would still remain mechanically bound to the casein, it would nevertheless be more finely subdivided and in this way its digestion would be favored

In order to test this hypothesis, a mixture of cows' milk containing approximately 3 per cent of fat was prepared and treated with rennet On attempting to rub the coagulum through a sieve it was found that a considerable portion did not pass through and when this portion was squeezed between the fingers it was found to contain fine, hard particles Professor Folin suggested that I add the rennet to the cream and prepare the mixture afterward

The required number of ounces of cream to give 3 per cent fat in the mixture was treated with rennet and it was then found that the entire coagulum could be pressed through the sieve and that, when squeezed between the fingers, it smoothed out without leaving hard particles When mixed with the other ingredients of the milk mixture it settled to the bottom of the nursing-bottle but with a somewhat larger aperture in the nipple, and by shaking the bottle occasionally during the feeding, very little remained behind The amount of fat not ingested did not exceed that of the other periods

COLLECTION OF FECES

The urine was not required for these observations, and a simple and effectual device was employed to prevent the admixture of urine and feces The penis was put through a small opening in a sheet of rubber dam The edge of the opening was fastened to the penis by a narrow strip of adhesive plaster The rubber dam was pinned to the mattress on either side Napkins were placed under and over the penis to absorb the urine

In previous metabolism observations I made use of a Bradford frame to collect the feces and urine This time I used a mattress such as the infant

was accustomed to A suitable opening was made in the mattress and the edges and several inches of mattress adjoining the edge on both sides were covered with rubber sheeting A wire tray was fastened to the bed beneath the hole and close to the mattress The wire tray held an oblong baking-tin a little smaller than the tray in which the feces were collected These pans could be removed and replaced merely by sliding them in and out of the wire tray During the observations the infant necessarily required more attention than usual and he was invariably cheerful when awake and slept normally

METHOD OF ANALYSIS

During the three metabolism periods the fat in the food was determined each day by the Soxhlet method Duplicate analyses were always made Following the method of Black for the determination of oxybutyric acid[1] in the urine, plaster of Paris was added to 20 c c of the milk with constant stirring until the desired consistency was reached It was then kept in the ice-chest until it could be analyzed It crumbled readily when dry and afforded a very simple and convenient method for determining the fat in milk

It was impossible by this method to make analyses of the rennet preparation agree, because of the unequal distribution of the fat The difficulty was overcome by accurately weighing and measuring a considerable quantity of the rennet milk mixture, evaporating this to dryness, reweighing the dried residue and then extracting the fat from weighed portions The total fat was calculated from this result In this way very close controls were obtained Sulphuric ether was used in the food analyses

The fat was determined in the feces by a method recently devised by Professor Folin[2] Some of the analyses of fat in the feces made last year by an older method did not check and so I discarded them all and applied to Professor Folin for a more accurate method Thus far the method has not been tested in substances other than feces and here it appears to give very accurate results Briefly described, Folin's method is as follows

The fat is extracted with acid ether prepared by passing dry hydrochloric acid gas into anhydrous ether (the degree of acidity is controlled by titration) The extract is evaporated to dryness and allowed to stand over night under petroleum ether The petroleum ether solution is carefully filtered, dried at a temperature under 100 C and weighed as total fat The fat is then dissolved in benzol, heated to boiling and titrated, while hot, against a standard solution

1 Black O F Jour Biol Chem 1908, v
2 Folin Jour Biol Chem, June, 1910

of metallic sodium in absolute alcohol, using phenolphthalein as indicator The end point is very sharply defined When a large quantity of fatty acid is present it is advisable to continue the heat during titration In this way the soap, which is formed, is kept in solution and permits of a sharp end point If it is desired to estimate the fat which is present in the form of soaps, then anhydrous sulphuric ether is used for a first extraction with subsequent treatment with petroleum ether, etc, as described above, and this is followed by a second extraction with acid ether, etc, thus making two procedures which are identical, including the titration, except that two solvents are used The first extraction removes the neutral fat and fatty acids the second extraction removes the soaps which have been converted into fatty acids

TABLE 1 —DETERMINATION OF FAT IN FECES

	Fat Ingested gm	Fat Absorbed gm	Dried Feces gm	Fat in Feces Per Cent	Neutral Fat in Feces, Per Ct	Fatty Acid in Feces, Per Ct	Fat Excreted gm	Fat Excreted, Per Cent
1st Period, March 4 to 6 — Breast-milk	83 2	74 3	26 5	33 4	06	27 4	8 8	10 6
2d Period, March 10 to 12 — Modified cow's milk	72	63 7	15 3	54 4	04	49 75	8 3	11 5
3d Period, March 15 to 17 — Modified cow's milk with rennet	72 3	64	15 7	52 75	05	47 75	8 3	11 5

GENERAL CONSIDERATION

Before discussing the results of this observation it is necessary to consider certain points in connection with the feeding which bear directly on the results

In the interval between the breast-milk and the first cows'-milk observation the baby was fed on breast-milk I intended to have the infant fed on the same mixture of cows' milk that was given during the second observation but concluded not to do so, because he previously had shown a lack of tolerance for cows' milk, and I wished to test his absorptive powers for cows' milk under the most favorable conditions A comparison of the second and third observations shows that the results were almost identical so that the interval of breast-milk feeding did not appear to exert any marked influence on the second observation I did not wish to test the tolerance of the infant for cows'-milk fat, but on the other hand. I desired him to ingest, if possible, an amount of fat compatible with a gain in weight In addition to this it was desirable for purposes of comparison that approximately the same quantity of fat should be ingested in each observation and it was improbable that the breast-milk would contain much less than 3 per cent of fat

At the hour selected to begin the first observation a Babcock test of the breast-milk showed 5 4 per cent of fat As the supply of breast-milk was limited I had the alternative of postponing the observations, with a very good chance that something else would occur to complicate matters or of using this milk for the first twenty-four hours and securing milk from another wet-nurse for the remaining forty-eight hours Under the circumstances it seemed wiser not to postpone the observation

At the end of the first twenty-four hours the infant was not so hungry as usual and left some of the milk On the next day the milk was obtained from another wet-nurse and contained 2 5 per cent of fat The baby's appetite returned and he showed no further signs of disturbance The excessive quantity of fat taken the first day may have influenced the subsequent absorption of fat The weight of dried feces during the breast-milk period very much exceeded that of either of the other two periods There is always an unknown and unavoidable error in the segregation of feces, but the difference between these periods appears to me to be larger than can be accounted for on this ground

CONSIDERATION OF RESULTS

The dried feces from the breast-milk period contained 33 4 per cent of fat, from the first cows'-milk period 54 4 per cent and from the second cows'-milk period 52 75 per cent This difference between the breast and cows'-milk periods is offset to a great extent when the total percentage of excreted fat is estimated If we assume that the fat in the feces represents fat that has been ingested, then 10 6 per cent of the ingested fat was excreted in the feces during the breast-milk period against 11 5 per cent during each of the cows'-milk periods I have little doubt that the absorption of fat during the breast-milk period was disturbed by the excessive quantity of fat ingested the first day, and that these percentages do not afford an accurate basis for comparison of the three periods If we consider the actual quantity of fat ingested and absorbed in each of the three periods an entirely different result is obtained During the breast-milk period the infant ingested 11 gm and absorbed 10 35 gm more fat than during either of the cows-milk periods In other words he absorbed 16 per cent more fat during the breast-milk period than during either of the cows'-milk periods It may be argued that if the cows'-milk fat had been raised to 5 4 per cent for one day, as was the case with the breast-milk, then the absorption of fat in the cows-milk periods would have equaled that in the breast-milk period This did not prove true in 1 patient with infantile atrophy fed on a cows'-milk mixture in which the fat was increased from 2 5 to 3 per cent the other ingredients and the

daily quantity remaining unchanged When the milk contained 2 5 per cent of fat the dried feces contained 41 per cent , when the milk-fat was raised to 3 per cent the dried feces contained 50 5 per cent of fat This was a marked increase in the excretion of fat following a relatively slight increase in the fat ingested Such a high percentage of cows'-milk fat as 5 4 if given to this atrophic infant, who had previously shown his inability to tolerate 3 per cent , would, in my opinion, have terminated the metabolism observation on the first day, owing to the disturbance which it would have caused in the digestion

The apparent intolerance for cows'-milk fat previously shown by this infant, the fact that so little digestive disturbance followed the administration of an excessive quantity of human milk-fat, and the much larger quantity of fat absorbed during the breast-milk period, may safely be accepted as evidence of a much greater tolerance for human milk fat than for cows'-milk fat Whether this difference is due to difference in the two kinds of fat or to the presence or absence of other ingredients in the two kinds of milk can be determined only by further experiments

It is interesting to note that only 4 or 5 per cent of the fat in the feces is present as neutral fat I have recently confirmed this observation in a number of normal and atrophic infants The rennet preparation of cows' milk did not appear to favor the absorption of fat as compared with a similar mixture of cows' milk without rennet

COMPARISON OF WEIGHTS

A comparison of the weights of the infant during the three metabolism periods cannot be made, because the caloric value of the breast-milk and cows'-milk mixtures was not identical It is interesting, however, to note the gain in weight that was coincident with the administration of breast-milk, which persisted as long as sufficient quantities of breast-milk were given, and that the tolerance for cow's milk became much improved during this time

The baby was under observation for twenty days previous to admission to the Massachusetts Infants' Asylum He was 13½ weeks old and presented the usual symptoms of infantile atrophy A tuberculin skin test was negative For the first three days of this period he was given a whey-and-cream mixture which contained 3 per cent of fat, and for the following nine days a similar mixture which contained 2 5 per cent of fat The food was then changed to a mixture of cow s milk which contained from 2 75 to 3 per cent of fat, 6 to 6 5 per cent of milk-sugar and 1 to 1 5 per cent of protein The daily quantity was 840 c c There was very little change in the weight during these twenty days—at the beginning

3,460 gm and at the end 3,450 gm The food was not well digested at any time and the baby vomited occasionally

He entered the Massachusetts Infants' Asylum February 18, at the age of 17 weeks, and was given a mixture of cows' milk for one day and a malt soup mixture for two days His condition was so bad at this time that he was given breast-milk From this date (February 21) to March 10 he was fed on breast-milk and gained in weight from 3,430 to 3,890 gm in seventeen days, that is, a gain of 460 gm The daily quantity of breast-milk ranged between 840 and 890 gm (28 to 29½ ounces)

Beginning March 10 he was given daily 840 c c of a modification of cow s milk which contained approximately 3 per cent of fat, 6 per cent of milk-sugar and 1 per cent of protein This was continued until March 21 The weight March 10 was 3,890 gm, and March 20 it was 3,950 gm, a gain of 60 gm in eleven days

Vomiting occurred on March 21 and for a time the baby was given alternate feedings of breast-milk and a whey-and-cream mixture March 23 his weight was 3,880 gm, and from this date until April 8 (eighteen days) the whey-and-cream mixture and breast-milk were continued in the proportion of one-third to one-half breast-milk An uninterrupted gain in weight occurred from 3,880 gm to 4,260 gm —380 gm

From April 8 to April 28 a modification of cow's milk containing approximately 3 per cent of fat, 6 per cent of milk sugar, and 1 per cent of protein was substituted for the whey-and-cream-mixture and alternated with breast-milk The baby continued to gain weight from 4,260 gm to 4,780 gm—520 gm in twenty days During the period from March 23 to April 28 the daily quantity of food varied between 925 and 1 000 c c April 28 he was 26½ weeks old and tolerated 3 per cent of cow s-milk fat in from one-half to two-thirds of the daily quantity of food ingested At this time the breast-milk was omitted and he was given 960 c c daily of a whey-and-cream mixture At the end of nine days the modification of cow s milk that previously had been tried was substituted for the whey-and-cream mixture and the baby was put out to board During these nine days he gained only 80 gm His tolerance for cow s-milk had improved so much that he was able to continue to take mixtures of cow s-milk and was sent home in the following September when he was 11 months old weighing 6 120 gm

I am glad of the opportunity to thank Dr I C Stowell for his great kindness in permitting me to carry out this investigation in the wards of the Massachusetts Infants' Asylum

In addition I wish to thank the superintendent Miss Cheney, and her assistant Miss Mabry for their supervision of the infant during the observations

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FURTHER INVESTIGATIONS IN EXPERIMENTAL MYOCARDITIS*

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A little over a year ago, we found that one single injection of 0 2 c c of adrenalin causes, in many cases, the appearance of a myocarditic lesion in rabbits,[1] and that the injection of small doses of spartein (0 012 gm per kilogram) or caffein (0 025 gm per kilogram), followed by the injection of a small quantity of adrenalin (0 2 c c of a 1 to 1,000 solution), produced macroscopic changes in the hearts of 60 per cent of the animals and microscopic changes in almost all cases We concluded therefrom that the typical effect of the intravenous injection of adrenalin was a cardiac and not an aortic lesion

I MYOCARDITIC LESION PRODUCED BY ONE INJECTION OF ADRENALIN

This method of producing a myocarditic lesion enabled us to study the sequence of the changes which resulted from these injections, by examining the animals at various periods after the single injection The changes which take place during the first six weeks we have already fully described, and, now, we desire to call attention to the changes noted at periods between six and twenty weeks after the injection

We published a preliminary report[2] concerning the changes noted in the rabbits' hearts at periods of from six to fifteen weeks after the injection, we shall here describe those changes more fully and, at the same time, review all the experimental work which we have so far carried on regarding myocarditic lesions Observations concerning the appearance of the myocarditic lesions at periods twenty weeks after the injection are here added The effects of two injections of spartein and adrenalin will

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1 Fleisher, M S and Loeb Leo Experimental Myocarditis THE ARCHIVES INT MED, 1909, iii 78

2 Fleisher, M S, and Loeb, Leo The Later Stages of Experimental Myocarditis Jour Am Med Assn 1909 liii 1561

also be described, as well as various other observations which have been made in the course of the study of these myocarditic lesions We shall first review in a brief manner the sequence of the changes noted in the first six weeks

Macroscopically, the lesion may be noted as early as two days after the injection, but it is most marked when seven or more days have elapsed The most common site of the lesion is the posterior wall of the left ventricle, close to the base and near the posterior interventricular sulcus The lesions vary considerably in size, but never affect the whole of the left ventricle The apex is usually not involved, but the papillary muscles frequently are The diseased area is pale and of a yellow brown color, as contrasted with the red brown of the normal cardiac tissue, it is stiffened and has lost its pliability and is usually thickened

Microscopically, the earliest change noted is separation of the muscle-fibers, and this may be found even a few minutes after the injection Two days later, the muscle-fibers may be separated and swollen, and the cross-strations seem to be a trifle paler than normally Not only are the muscle-fibers increased in size, but the nuclei, also, are larger Even at this early period, the number of young connective tissue cells between the muscle-fibers is increased

In the next few days the changes become more pronounced The separation of the muscle-fibers which is probably due to edema, is marked In places, degenerative changes in the muscle fibers may be noted, some fibers appear to have been dissolved, leaving only a thin ring of muscle substance surrounding the nucleus, in other places, the fibers are hypertrophied, and at other places, they contain vacuoles of various sizes

At the period between twelve and twenty-one days after the injection the changes have reached their maximum The increase of connective tissue is now diffuse, especially marked around the blood-vessels and around the endocardium and pericardium, but it is also present between the muscle-fibers The degenerative changes have also progressed, there are small areas in which the muscle-fibers are more or less dissolved and, throughout the fibrillar connective tissue network which is left, are scattered the nuclei of the muscle-fibers surrounded by a pale ring of muscle substance Most of the muscle-fibers are increased in size, although occasionally an atrophic fiber is noted showing an increase of the perinuclear pigment The transverse strations have become less clear but are not completely destroyed Vacuoles within the cells are more frequent but can by no means be said to be common they appear usually in the cells near the endocardium but are not confined exclusively to this portion of

the heart The nuclei are larger than usual and the appearance of double nuclei within the cells is more frequent

Microscopically, we find that the interstitial changes begin soon after the injection and become steadily more marked, in the early periods, they are only noticeable around the blood-vessels, endocardium and pericardium, later, all the connective tissue elements take part in the proliferation In the parenchyma the principal and earliest change noticeable is an increase in size of the muscle-fibers and, associated with this, is an increase in size of the nuclei and increase in the number of the double nuclei

We have noted the changes in the connective tissue very shortly after the injection, and usually at a time when no marked degenerative changes were noted in the musele-fibers Thus, at a period twenty-four hours after the injection, there was separation of the muscle-fibers, that is, edema of the supporting tissue and forty-eight hours after the injection, we have noted an increase of the young connective tissue cells At this time the only change noted in the muscle-fibers was an increase in size, due probably to edema, and, in the sections examined, we found no marked degenerative changes in the muscle-fibers, such as paling of the cross-striations and vacuolization, until the third or fifth day We do not necessarily conclude from these results that the connective tissue changes always appear earlier than the degenerative changes, for there may be some cases in which the degenerative changes appear at an earlier stage than we have noted them Whether the prolifeiative connective tissue changes are primary, or whether they are secondary to changes in the musele-fibers (edema of the musele fibers), we cannot state with certainty, but it would seem that the early interstitial changes are in many cases not secondary to the parenchymatous changes, but result from the edema which is noted very shortly after the injection Therefore, it is probable that the early interstitial and parenchymatous changes are usually independent of one another, and that they are due to one and the same causal factor

We have already called attention to the fact that the lesions produced by the injection of spartein or caffein and adrenalin are essentially the same as lesions noted in hearts of animals in which cardiac hypertrophy had been produced experimentally, or in cases of hypertrophy of the human heart as found at autopsy

Altogether we have examined the hearts of one hundred and twenty rabbits killed at various periods within the first six weeks after the injection of spartein and adrenalin, and we have found gross myocarditic lesions in 63 per cent Forty-six rabbits have been examined at various periods later than six weeks after the injection and only 22 per

cent showed macroscopical myocarditic lesions These were examined eight, ten, fifteen, and twenty weeks after the injection Myocarditic lesions were found in between 22 per cent and 27 per cent of the rabbits examined at eight, ten, and fifteen weeks, but in only 15 per cent of those examined after twenty weeks

When a myocarditic lesion is present at ten to twenty weeks after the injection, it is usually smaller, and shades more gradually into the normal tissue than those noted at earlier periods The loss of pliability of the ventricular wall is still noticeable, but only rarely is the wall thickened In short, the lesion appears to be retrogressing

On microscopical examination, changes are noted even in those hearts which show no lesion macroscopically But even the microscopical lesions are much less marked at eight weeks than those at the earlier periods The hypertrophy of the muscle-fibers is less marked, and fewer double nuclei are noted The connective tissue increase is still diffuse and, in a few places, there appear areas of connective tissue replacing degenerated muscle-fibers Most of the degenerative changes have disappeared and it is only rarely that vacuolization of the muscle-fibers is found

At periods from ten to fifteen weeks after the injection, the hypertrophy of the muscle-fibers has all but disappeared and the number of double nuclei is no longer increased Neither vacuolization of the muscle-fibers nor paling of the cross-striation is noted at this period The connective tissue has now begun to become fibrous In some areas there appear tracts of rather dense fibrous tissue containing what appear to be the remnants of degenerated muscle-fibers In other areas infiltrations with small cells may be seen The fibrous areas are not diffuse, but are scattered, here and there, throughout the heart Such areas are usually small, but a few fairly extensive areas are occasionally seen in the central portion of the ventricular wall, or near the endocardium and occasionally in the papillary muscles

In the hearts examined twenty weeks after the injection the conditions are very similar to those just described However no degenerative or hypertrophic changes are visible The increase of connective tissue is the only abnormal feature At all places the new connective tissue is becoming fibrous In the central portions of the heart wall small areas of fibrous tissue separating the muscle-fibers are noted at other places most commonly near the endocardium and at the base of or in the papillary muscles areas of connective tissue seem to have replaced the degenerated muscle-fibers these areas are usually small In other places small connective tissue cells are scattered between the muscle-fibers In some hearts these changes are quite extreme in others almost no changes are

noted, in only one of the eleven hearts examined microscopically twenty weeks after the injection, could no changes whatever be seen On the whole, the connective tissue appears to be slightly less at this period than in hearts examined ten or fifteen weeks after the injection

At twenty weeks the connective tissue is, therefore more fibrous, but is not so extensive nor is it so diffuse as it was at earlier periods

At a period six weeks after the injection of spartein and adrenalin, practically all of the preexisting connective tissue shows activity and, throughout the ventricular wall, between the muscle-fibers, about the vessels and near the endocardium, the number of young connective tissue cells is increased Eight, ten, or fifteen weeks after the injection, the connective tissue increase is less diffuse and has become confined to small areas in the central portion of the ventricular wall, or in the base of the papillary muscles or in the papillary muscles themselves Furthermore the connective tissue is becoming fibrous At a period twenty weeks after the injection, we find only a few scattered areas of fibrous tissue which, in most cases, appear to be replacing atrophic or degenerated muscle-fibers These areas of connective tissue are smaller than those noted at eight, ten, or fifteen weeks and, on the whole, there is less connective tissue present twenty weeks after the injection, than six weeks after the injection

The interstitial changes appear to have reached their maximum about six weeks after the injection and, from this time onward, the connective tissue changes grow less marked, until the only signs of the connective tissue overgrowth are the fibrous areas replacing the degenerated muscle-fibers Thus, the only places in which the increased connective tissue persists are those where its increase has been secondary to the degenerative changes It is of considerable interest to observe that an actual connective tissue increase may apparently disappear entirely in certain parts of the heart wall We expect, however, to extend our investigations into the ultimate fate of the connective tissue, and we do not regard our conclusions as final, as far as the diminution in the amount of connective tissue is concerned

It is also of interest to note that twenty weeks after the injection, all degenerative changes have disappeared and in only a few small areas do we find evidence that connective tissue has replaced the degenerated musele-fibers In an effort to determine whether any regenerative changes could be noted in the muscle-fibers, we have examined the apex and septum as well as the site of the lesions, but we found no evidences of regeneration or compensatory hypertrophy, it is, therefore probable that the less pronounced degenerative changes in the muscle-fibers rarely lead to the

actual destruction of the muscle-fibers and that a recovery of the muscle-fibers may take place in many cases

Thus, in spite of the rather severe changes noted in both the parenchyma and the interstitial tissue of the heart at a period shortly after the injection of spartein and adrenalin, we find that in a relatively short time, these changes disappear and only very slight evidence is left of the earlier presence of any pathological condition It appears that the myocarditic lesion actually heals and that in many cases the repair is not due to the replacement of the injured parenchyma by fibrous tissue but by a recovery of certain muscle-cells

II EFFECT OF SECOND INJECTION OF ADRENALIN

Thus far, we have spoken only of the influence of a single injection of spartein and adrenalin It was of interest to determine in what manner a second injection of spartein and adrenalin influenced the frequency and the severity of the myocarditic lesions

We find that when rabbits are injected with spartein and adrenalin on two successive days, 54 per cent of them show gross myocarditic lesions two weeks after the last injection When the two injections are separated by a period of two weeks, 53 per cent of the rabbits develop lesions In none of these cases are the lesions more extensive than after one injection, and the microscopic changes are also similar to those noted after a single injection When a period of nine weeks elapses between the first and second injection 83 per cent of the animals show myocarditic lesions, 25 per cent, however, show retrogressing lesions, while only 58 per cent show fresh lesions

It appears, therefore, that the first injection is of the greatest importance in causing the appearance of the lesion and that the giving of two successive injections does not increase the occurrence of the lesions provided the second injection be given before the lesions are fully developed or at the time of their full development If, however the second injection is given at a time when the lesions have begun to retrogress the second injection causes the appearance of new myocarditic lesions in the usual percentage of the animals injected irrespective of whether lesions had or had not resulted from the first injection No increase in resistance no immunity has therefore been conferred on animals that have recovered from the effects of a first injection

III EFFECT OF ADRENALIN AND SPARTEIN ON KIDNEYS

In an earlier communication we stated that no renal lesions were noted as a result of the injection of adrenalin and spartein Since then

we have carried further our investigation regarding the influence of these injections on the kidneys We collected the urine secreted by the injected animals, and compared the quantity secreted by these animals in twenty-four hours with the quantity secreted by normal animals We also made tests for albumin in the urines of the injected animals

The quantities of urine secreted by the individual rabbits varied considerably, but, in general, no differences were noted between the amounts of urine secreted by normal and injected rabbits The degrees of the individual variations, as well as the average amounts of urine secreted, were approximately the same in both series

Among twenty-six injected rabbits, half of which had been injected twice, five showed albuminuria Two of these five had pneumonia and pleurisy and in these cases the infection probably caused the albuminuria, two others showed but a faint trace of albumin in the urine It seems hardly probable that the albuminuria in the three cases was due to a renal lesion produced by the injection of spartein and adrenalin, since some apparently normal rabbits also eliminated albumin in their urine Thus it appears that the injection of spartein and adrenalin does not interfere with the functions of the kidney under otherwise normal conditions

IV INFLUENCE OF MYOCARDITIC LESIONS ON SECRETION OF URINE

We have likewise tested the influence of these experimental myocarditic lesions on the secretion of urine, the production of peritoneal transudate and the blood-pressure [3] We found that, in rabbits with myocarditic lesions, the arterial blood-pressure is slightly lower than usual, furthermore, that such rabbits are not as well able to resist the injurious effect of the intravenous infusion of large quantities of 0 85 per cent sodium chlorid solution as normal rabbits, and that in rabbits with heart lesions such an infusion leads to a gradual steady fall of the arterial pressure Although the amount of peritoneal transudate resulting from such hydremic plethora was not influenced by the presence of a myocarditic lesion, the elimination of the infused fluid through the kidneys was markedly diminished in rabbits with myocarditic lesions This lessened elimination was probably due to the lowered blood-pressure which resulted from the inability of the diseased heart to respond to the extra strain put on it by the increased bulk of fluid within the vessels

V INFLUENCE OF MYOCARDITIC LESIONS ON EDEMA OF LUNGS

It has likewise been noted[3] that when animals with myocarditic lesions were infused with large quantities of sodium chlorid solution or sodium-

3 Fleisher M S and Loeb, Leo Jour Exper Med, 1909 xi 480 627 641

chlorid-calcium-chlorid solution, edema of the lungs appeared more frequently than when normal animals were subjected to similar infusions It may be that the more frequent occurrence of edema of the lungs in animals with myocarditic lesions is due to the disproportionate amount of work being done by the two ventricles, thus, while the right ventricle discharges a normal or increased amount of blood into the pulmonary arteries (increased because of the hydremic plethora), the diseased left ventricle might be unable to discharge the same amount of blood into the systemic vessels, and, as a consequence, the pulmonary circulation would be overfilled If this explanation of the sequence of events be correct, the above results would appear to support the mechanical explanation of the occurrence of pulmonary edema

VI INFLUENCE OF MYOCARDITIC LESIONS ON ASCITES

At the present time, we are carrying out a series of experiments in which we are testing the influence of myocarditic lesions on the production of edema and, especially, ascites in animals poisoned with uranium nitrate Our results, so far, point to the conclusion that the presence of a myocarditic lesion increases the amount of ascitic fluid in animals poisoned with uranium nitrate, in spite of the fact that the secretion of urine is also increased Our experiments, however, are as yet not sufficiently numerous for us to draw a definite conclusion

VII INFLUENCE OF SPARTEIN AND ADRENALIN ON PERICARDITIS

In a few of the injected animals we have found pericarditis Thus, in three different lots of rabbits, including in all forty-two individuals, we have found six rabbits with pericarditis, in no other rabbits, either those injected with spartein and adrenalin (in all about 116 animals) or normal rabbits which were examined in the course of other experimental work, have we found similar conditions Three of the six rabbits were in the series of animals which were examined twenty weeks after the injection, two showed not only a marked fibrinous pericarditis but also bilateral pneumonia and fibrinous pleurisy one of these showed a very slight gross myocarditic lesion while the other showed none The third animal of this lot which showed pericarditis had no associated pulmonary lesion and no demonstrable gross myocarditic lesion in this case the pericardial condition consisted of a rather firm adhesion between the parietal and visceral pericardium over the base of the left ventricle and the lower part of both auricles, the process had here evidently healed In all three of these cases microscopic evidences of myocarditic changes were noted

In another lot of rabbits that had received two injections separated by an interval of one week, two showed a fibrinous pericarditis at a period fourteen days after the second injection Both of these animals had also pleurisy and pneumonia and showed marked myocarditic changes to the naked eye

In a third lot of rabbits which received only one injection of spartein and adrenalin (these were rabbits which were to have received a second injection at a period nine weeks after the first one), five weeks after the injection, one animal showed fibrinous pericarditis which was associated with a marked gross myocarditic lesion as well as with pneumonia and pleurisy One other animal which died at the same time showed both myocarditis, and pneumonia and pleurisy, but no pericarditis

The pericarditic condition noted in the above-mentioned cases was as a rule not localized over the left ventricle, but the fibrin deposit appeared on all parts of both ventricles and also on the auricles In view of the almost constant association of pneumonia and pleurisy with the pericarditis, it appears improbable that the myocarditic lesion was the direct cause of the pericarditis, or that the injection of adrenalin and spartein produced the pericarditic lesion in the same direct way as it did the myocarditis In some cases the pneumonia and pleurisy may have preceded the pericarditis, it seems, however, very probable that the myocarditic lesion rendered the animal more susceptible to a bacterial infection, which latter was directly responsible for the pericarditis, pleurisy and pneumonia

The myocarditic lesion probably created a condition favorable to a bacterial infection of the pericardium and by interfering with the pulmonary circulation it may, moreover, have indirectly prepared this soil for a bacterial infection of the lungs

VIII EXCESSIVE MECHANICAL STRAIN THE CAUSE OF MYOCARDITIC LESIONS

We have already expressed our belief that excessive mechanical strain is the direct cause of these myocarditic lesions The fact that the seat of the lesion is close to the auriculoventricular junction near the place of insertion of the muscle-fibers of the left ventricle, where naturally the greatest strain would be exerted, as well as the fact that the lesions are confined to the left ventricle, appear to support this view

Furthermore, it has been shown in this laboratory, by one of us working with Dr Strickler,[4] that, although the injections of spartein and

[4] Strickler and Fleisher Jour Pharm and Exper Therap 1910 II, No 1

adrenalin will generally produce the same symptoms in dogs as in rabbits, such injections do not cause the appearance of myocarditic lesions in dogs whose hearts are relatively stronger than the hearts of rabbits It is interesting that in rabbits both arterial and myocarditic lesions can be produced by the injection of adrenalin, while in dogs neither of these changes can be produced

According to our theory, the myocarditic changes are not due to contraction of the coronary vessels and consequent lack of nutrition in the muscle-fibers The site of the lesion, as mentioned above, as well as the behavior of the coronary vessels,[5] which are not supposed to contract under the influence of adrenalin, speak against such a theory But we believe that the appearance of the lesion is due to the excessive contraction of the muscle-fibers of the heart It has been shown that excessive contraction of striated muscles causes[6] these to take up more fluid, and, after the injection of adrenalin and spartein, we have found edema of the heart muscle, a condition analogous to that noted in the striated muscle

CONCLUSIONS

1 The injection of one single dose of spartein or caffein with adrenalin causes the appearance of gross myocarditic lesions in 60 per cent of the rabbits injected, and the appearance of microscopic lesions in the hearts of almost all the rabbits

2 The lesions appear a few days after the injection The earliest change (separation of the muscle-fibers due to edema) may be noted a few hours after the injection The gross lesion may become apparent a few days after the injection

3 The lesions consist in their earlier stages (up to a period of six weeks after the injection) in a combination of the following changes (a) increase of connective tissue which appears very early and is quite diffuse (b) hypertrophy of the muscle-fibers, with increase of the double nuclei of the muscle cells and indistinctness of the cross-striation the first of these appearing approximately as soon as the interstitial tissue changes, (c) marked degenerative processes affecting the muscle-fibers which are most marked at the later period of this stage of the disease and which seem to appear later than the interstitial and hypertrophic (edematous) changes It seems probable that the interstitial and parenchymatous changes develop independently of each other at least at first It

5 Langendorff Ztschr f Physiol, 1907, xxi 351

6 Ranke Tetanus Leipsic, 1865 Cooke Jour Physiol 1898, xxiii 137 Fletcher Jour Physiol 1901, xxv, 111 Loeb, J Arch f d ges Physiol 1901 lvi, 270

later stages parenchymatous degeneration induces connective tissue proliferation

4 At later periods, namely, from eight to twenty weeks after the injection, a gradual disappearance of the changes in the muscle-fibers is observed The hypertrophy, increased number of double nuclei and indistinctness of the cross-striations gradually disappear The more marked degenerative changes also disappear and only a few areas remain in which some atrophic muscle-fibers are noted The connective tissue changes become less marked and less diffuse Finally, at a period twenty weeks after the injection, the only evidence of the myocarditic lesion noticeable consists in some small fibrous areas which contain the remnants of atrophic muscle-fibers, it is, therefore certain that these areas of fibrous tissue replace degenerated muscle-fibers and that the connective tissue increase in these areas has been secondary

5 The disappearance of the degenerative changes in the muscle-fibers does not seem to be due to an ingrowth of muscle-fibers from the surrounding normal tissue into the degenerated areas but seems largely to be due to the recovery of those muscle-fibers in which the changes had not been very pronounced, at least, we were not able to recognize any evidence of regenerative processes in the muscle cells [7]

6 When animals which have received one injection of spartein and adrenalin are given a second injection, we find evidence neither of immunity nor of increased susceptibility to the effects of a second injection Animals which received two injections, separated by intervals of either twenty-four hours or one week, showed relatively the same number of lesions as animals which received only one injection Animals which received the second injection nine weeks after the first one—thus, at a time when the lesions were retrogressing—developed myocarditic lesions as a result of the second injection in approximately the usual percentage of cases, in such animals, retrogressing lesions which had resulted from the first injection were noted as well as the fresh lesions due to the second injection In no case did the myocarditic lesions resulting from two injections differ to any marked extent, either macroscopically or microscopically, from those resulting from one single injection

7 The hearts which show macroscopic lesions we found to be functionally inferior to normal hearts, inasmuch as they are unable to meet successfully a demand for extra work

7 Whether or not the increase in the number of double nuclei in the muscle cells indicates a regenerative process, we can not decide until we find distinct evidence of a multiplication of the muscle cells

8 It seems probable that in animals with myocarditic lesions the injection of uranium nitrate and of large quantities of water leads to an increase in the amount of ascitic fluid Our experiments in these directions are, however, as yet not sufficiently extensive to permit us to draw a definite conclusion

9 The presence of a myocarditic lesion may favor indirectly the occurrence of a fibrinous pericarditis, pleurisy and pneumonia by preparing the soil for a bacterial infection The injection of adrenalin and spartein is in all probability not the direct cause of the development of pericarditis

10 We believe that excessive mechanical strain is the direct cause of the myocarditic lesions The typical seat of the lesion, at the base of the left ventricle, where the greatest strain is exerted, favors this theory Furthermore, analogous conditions have been shown to occur in striated muscle in conditions of over exertion The fact that the injection of spartein and adrenalin into dogs whose hearts are relatively stronger than those of rabbits, does not cause the appearance of myocarditic lesions, adds further support to this theory These lesions are, in all probability not due to a lack of nutrition of the muscle-fibers as a result of the contraction of the coronary vessels, inasmuch as it has been shown that adrenalin does not cause a contraction of the coronary vessels

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THE EFFECT OF PERMANENT CONSTRICTION OF THE SPLANCHNIC ARTERIES AND THE ASSOCIATION OF CARDIAC HYPERTROPHY WITH ARTERIOSCLEROSIS

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PHILADELPHIA

The importance of arteriosclerosis as a cause of cardiac hypertrophy is a problem which for many years has attracted the attention of both pathologists and clinicians, but even after the most extensive studies on the subject one must admit that the question is, as yet, far from settled The great obstacle to the elucidation of this problem has been the difficulty in obtaining an exact method for study So far, most of our conclusions have been drawn from the examination of autopsy material and it is well known how many and what complicated factors confront one under these circumstances Diseases of the blood-vessels are so frequently associated with other conditions, such as chronic nephritis, which of themselves may lead to hypertrophy, that it is with the greatest difficulty that one can make accurate deductions concerning the direct influence of arteriosclerosis

It seems, however, to have been shown satisfactorily that sclerosis of the peripheral vessels is not necessarily accompanied either by an increase in blood-pressure or hypertrophy of the heart On the other hand it has been quite generally assumed, since the publication of the work of Hasenfeld[1] and Hirsch[2] that arteriosclerosis of the thoracic and abdominal aorta, and especially narrowing of the lumina of the splanchnic arteries, may be a potent factor in the causation of cardiac hypertrophy Though Marchand states that he could not, from his own experience confirm this view, it may nevertheless be said that the careful observations, especially of Hasenfeld and Hirsch, have done much to substantiate this claim

But the question has not been put to experimental test It was, therefore the object of the present study to attempt first, to reproduce as nearly as possible by experimental methods a narrowing by arteriosclerotic processes of the lumen of the celiac axis and superior mesenteric artery,

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*From the Department of Applied Medicine University of Pennsylvania

1 Hasenfeld Deutsch Arch f klin Med, 1897, lix 193

2 Hirsch Deutsch Arch f klin Med, 1899, lxiv 579

3 Marchand Verhandl d Cong f Inn Med 1904 xxi 60

and, secondly, to study subsequently the effect of this operation on the blood-pressure and heart In some previous experiments it was found that constriction of either the superior mesenteric artery or celiac axis in dogs caused an immediate rise in blood-pressure of from 8 to 22 mm of Hg with an average of 14 mm Hg, while constriction of the two arteries at the same time about doubled this rise The rise in general blood-pressure was moreover not fleeting, but persisted in some experiments for at least an hour

It was thought, therefore, quite possible that permanent constriction of these arteries might be accompanied by a continuous increase in blood-pressure with the development of cardiac hypertrophy

For the following experiments dogs were used exclusively The animals were etherized and the abdomen opened to the right or left of the mid-line, sometimes directly in the mid-line The superior mesenteric artery and celiac axis were dissected free from the dense plexus of nerves which surrounds them as they branch from the aorta, and, by means of the ingeniously devised instrument described by Halsted,[4] aluminum bands 3 to 4 mm in width were rolled about the vessels These bands were then tightened about the arteries with the finger until the pulsation in the distal side was greatly reduced in force, or almost obliterated The wound was then closed

At intervals covering months after the operation, the blood-pressure of the dogs was studied For this purpose the cuff devised by Janeway[5] was employed attached to a Stanton manometer Owing to the fact that the proper apparatus was at first not obtained, and to the fact that some time was required to develop our technic, the blood-pressure of the dogs during the early experiments was not estimated before the operation Later however, estimations were made before the operation often several times, as controls for the later readings

Bands were thus placed either about the superior mesenteric artery alone or both the superior mesenteric artery and celiac axis of sixteen dogs Seven of these dogs died within a week of the operation, two from pneumonia and five from infarction of the intestines following thrombosis of one or both of the constricted arteries One dog died on the eleventh day of a phlegmon of the stomach and one on the thirteenth day of pneumonia Several dogs have been studied over a period of from three

4 Halsted Jour Exper Med, 1909, xi, 373 The band rollers and aluminum were kindly loaned by Dr Halsted

5 Janeway Proc Soc Exper Biol and Med, 1909 vi 105

to five months In four dogs the superior mesenteric artery alone was constricted, in five dogs both vessels were surrounded by bands The following is an abstract of the protocols of the last nine dogs

Dog 279—Fox terrier type, male, weight 24 pounds
November 9, 1909 Operation, band placed about superior mesenteric artery, fair pulse in arteries of omentum Dog recovered well, lost weight
November 29 Weight 23 pounds, thin, but eating well
December 7 Weight 23 pounds Stools hard and black
December 29 Weight 22½ pounds
January 12, 1910 Weight 21½ pounds
January 17 Systolic pressure 130 to 118
January 20 Weight 23½ pounds
January 31 Systolic pressure 125 to 112
February 3 Weight 25 pounds
April 15 Systolic pressure 135 to 118
April 22 Systolic pressure 115 to 130
April 25 Dog killed Band closely approximated about artery, but lumen patent, though tightly constricted All the organs are normal
Dog 280—Fox-terrier type, male, weight 18 pounds
November 17 Aluminum band placed about superior mesenteric artery
November 29 Dog thin, stitch abscess
December 1 Weight 17 pounds, eats well
December 10 Weight 18 pounds, in good condition
January 12 Weight 19 pounds
January 17 Systolic pressure 100 to 125
February 3 Weight 18½ pounds
April Dog lost
Dog 276—Male, weight 18 pounds
October 26 Operation, band placed about superior mesenteric artery
November 4 Dog not well, wound healed, languid
November 8 During last few days stools dark brown and soft, losing weight Dog died November 8 of pneumonia with purulent pleurisy, congestion of intestines and liver, the band is in place and shows tight constriction of vessel which is patent
Dog 282—Black and tan, male
November 22, 1909 Aluminum band placed about superior mesenteric artery
November 29 Dog doing well
December 1 Weight 22 pounds
December 7 Weight 20 pounds, stools seem normal
December 15 Systolic pressure 85, weight 22 pounds
January 12, 1910 Dog in good condition, weight 21 pounds
January 14 Systolic pressure 70 to 80
January 26 Systolic pressure 78 to 82
February 3 Weight 20½ pounds
April 5 The dog has bad mange, systolic pressure 85 to 100
April 16 Dog killed The band is tightly placed about superior mesenteric artery and the vessel is completely converted into a fibrous cord
Dog 283—Small white fox-terrier, male, weight 13 pounds
November 10, 1909 Operation band placed about superior mesenteric artery
December 7 Stools soft and dark weight 11 pounds, does not eat well
December 15 Improving, weight 10 pounds, stools soft and dark

January 5, 1910 Weight 12 pounds
January 12 Weight 14 pounds
January 26 Systolic pressure 90 to 95
February 3 Weight 15 pounds
April 5 Systolic pressure 85 to 100 Dog in rather poor condition
April 6 Dog killed on account of mange The superior mesenteric artery is converted into a fibrous cord and completely occluded The organs are normal Berlin blue injected into the femoral artery reaches the entire small intestine before it colors the stomach

Dog 208.—Brindle, male

December 7, 1909 Operation, aluminum bands placed about superior mesenteric artery and celiac axis, marked thrill on distal side of bands
December 8 Systolic pressure 95 to 105
December 10 Good condition, stools lost, weight 28 pounds
December 15 Weight 27 pounds, systolic pressure 120 to 125, there is a diarrhea
December 29 Systolic pressure 85
January 5, 1910 Weight 27 pounds
January 12 Weight 26 pounds, condition good
January 14 Systolic pressure 95 to 102
January 22 Stools again normal
January 26 Systolic pressure 95 to 100
February 3 Weight 27 pounds
April 5 Dog is thin and has the mange, systolic pressure 105 to 110
April 18 Dog killed Both bands in place and both arteries patulous, though the lumina are constricted

Dog 290.—Large black and white, male, weight 36 pounds

December 15, 1909 Systolic pressure 115 to 120
December 17 Systolic pressure 113 to 120
December 18 Systolic pressure during operation 107 to 115 Operation, bands placed about superior mesenteric artery and celiac axis, immediately after bands in place systolic pressure 115 to 125
December 20 Dog in good condition, pressure cannot be obtained
January 5, 1910 Weight 32 pounds
January 14 Systolic pressure 128 to 132
January 20 Weight 34 pounds
January 26 Systolic pressure 128 to 132
February 3 Weight 35 pounds
February 15 Systolic pressure 128 to 130 Soft brown stools
March 14 Dog killed The celiac axis is completely converted into a fibrous cord, the superior mesenteric artery is surrounded by the band the lumen is narrowed to almost pin hole size but patulous, the organs are normal

Dog 293.—Brown, fairly large male, weight 26 pounds

January 10 Systolic pressure 90 to 93
January 11 Systolic pressure 92 to 87 Operation, bands placed quite tightly about superior mesenteric artery and celiac axis, scarcely any pulsation felt in distal part of artery
January 12 Dog in good condition, systolic pressure 71 to 77
January 17 Systolic pressure 110 to 112
January 20 Weight 20 pounds
January 21 Dog developed bloody stools, vomited blood and died

The stomach shows hemorrhagic phlegmon, the intestines are intensely congested, the bands surround the celiac axis and superior mesenteric artery and seemingly constrict the lumen, but do not occlude it

Dog 294—White pointer, large male, weight 30 pounds
January 10 Systolic pressure 92 to 107
January 17 Systolic pressure 98 to 112
January 18 Operation, bands put about celiac axis and superior mesenteric artery
January 20 Dog in good condition, weight 30 pounds
January 24 Systolic pressure 111 to 124, wound not healing well
January 31 Wound in much better condition, systolic pressure 115 to 130, weight 24½ pounds
February 7 Systolic pressure 90 to 100
April 15 Systolic pressure 120
April 22 Systolic pressure 120 to 110
April 27 Dog killed The organs are normal except for some congestion of the liver The superior mesenteric artery and celiac axis are tightly surrounded by the bands, and the lumina are constricted to pin-hole size, but patulous

Immediately after the operation all the dogs rapidly lost weight, but in many instances this was soon regained Digestive disturbances were frequent A few dogs developed diarrhea with soft dark stools, one dog died with extensive phlegmonous gastritis

The effect of constricting the superior mesenteric artery and celiac axis may be seen in Table 1

TABLE 1—EFFECT OF CONSTRICTION OF SPLANCHNIC ARTERIES ON BLOOD-PRESSURE *

No	Operation Date	Arteries Constricted	December 8	December 15	December 17	December 18	December 29	January 10	January 11	January 14	January 17	January 18	January 24	January 26	January 31	February 7	February 15	February 16	February 21	April 5	April 15	April 22	Death, Date
279	11/ 9	Sup mesent			123										114						124	121	4/23
280	11/17	Sup mesent									113												Lost
282	11/22	Sup mesent								76				81						97			4/16
283	11/30	Sup mesent												91						90			4/ 6
288	12/ 7	Sup mesent and celiac axis	100	122			85			98				97						102			4/16
290	12/18	Sup mesent and celiac axis		117		119				130				129			129						3/14
293	1/11	Sup mesent and celiac axis						92	92		112												1/21
294	1/18	Sup mesent and celiac axis						102	105				117		124	95					120	115	4/27
295	2/15	Sup mesent and celiac axis									116		102		119		98		102				2/23

* The numbers are the averages of 6 to 12 separate readings The systolic pressure is computed from the moment that the pulse in the paw disappears

It is evident that there is no definite change in the blood-pressure following these experiments In Dogs 290, 293, and 294 there is a slight rise varying from 11 to 19 mm Hg after the operation but the elevation

is not constant and is not sustained In no instance did the blood-pressure rise above a limit which is reached by normal dogs, as could be determined in control experiments Except for the transient disturbances described, no ill effects on the health of the dogs could be observed

After periods varying from four to six months the dogs were killed and their hearts weighed by Muller's[6] method Table 2 gives the results of this analysis, which may be compared with the figures from twenty-eight normal dogs used as controls

TABLE 2—RATIO OF BODY WEIGHT TO WEIGHT OF WHOLE HEART AND VENTRICLES IN 28 NORMAL DOGS

No	Operation	Duration of Experiment	Condition at Death	Weight of Dog in gm	Whole Heart in gm	Proportion	Ventricles in gm	Proportion
298	Sup mesent and celiac axis	1 day	Fair	13,610	109 5	0080	99 5	0073
297	Sup mesent and celiac axis	7 days	Fair	7,460	64 0	00857	56 0	0075
295	Sup mesent and celiac axis	7 days	Fair	13,560	122 5	0090	111 0	00818
293	Sup mesent and celiac axis	11 days	Wasted, lost 6 lbs	8,400	84 5	010	77 7	009
283	Sup mesent	4 mos , 7 days	Emaciated	5,520	51 0	0092	44 1	00797
290	Sup mesent and celiac axis	3 months	Fair	14,500	117 5	0081	104 0	0071
279	Sup mesent	5 mos , 24 days	Good	11,500	85 5	00743	77 5	00656
282	Sup mesent	4 mos , 24 days	Fair	9,100	65 9	00724	59 5	00653
288	Sup mesent and celiac axis	4 mos , 11 days	Fair	11,640	82 5	00709	75 3	00647
294	Sup mesent and celiac axis	3 mos , 9 days	Good	11,000	90 0	00818	79 9	00724

The ratio of body weight to weight of whole heart varied from 0063 to 0089
The ratio of body weight to weight of ventricles varied from 0055 to 0078

When the ratios of the weights of the whole heart and of the ventricles to the body weight of these dogs are examined it is immediately seen that, except for three instances, they fall well within the normal limits The ratio for the whole heart in the operative series varied between 0 00709 and 0 0086 and for the ventricles between 0 00647 and 0 0075 In twenty-eight normal dogs, used as controls the figures for the whole heart varied between 0 0063 and 0 00898 and for the ventricles between 0 0055 and 0 00782 Two of the three dogs of the operative series died seven and eleven days, respectively after the operation and the slight increase in the ratio is unquestionably due to the rapid loss in body weight following operation The third dog which showed the high ratio was killed four months and seven days after operation During the last week or ten days of his life however he had lost weight very rapidly which again

6 Muller Die Massenverhältnisse des menschlichen Herzens, Hamburg 1855

may account for the comparatively high figure In all the dogs the valves were carefully examined in order to exclude any accidental valvular lesions which might lead to hypertrophy

Four dogs died within two weeks of the operation In three of these, though there was no thrombosis of the arteries constricted, a marked congestion of the stomach, intestines, spleen and liver was found In two cases this may have been due in part to the acute infection of the lungs which was present, but in one dog this factor could be eliminated In the fourth dog there was thrombosis of both vessels, but there was no actual infarction of the intestines or of the other viscera From previous observations and from the clinical symptoms which some of these dogs presented during the first week or two after operation (diarrhea with soft, dark bowel movements) we are led to the conclusion that the first effect of diminishing the arterial blood-supply to the intestines and liver by narrowing the lumen of the superior mesenteric artery and celiac axis is not an anemia, but a congestion of the organs supplied by these vessels

After complete occlusion of these vessels hemorrhagic infarction develops During this process, the blood arrives in the intestines by way of the slight collateral anastomosis which the superior mesenteric artery makes with the inferior mesenteric If, however, the occlusion of these vessels is not complete there is still sufficient pressure in the distal portion of the arteries to prevent complete hemorrhagic necrosis of the intestines, but not enough to maintain a normal circulation The result is, therefore, an immediate congestion in this region But an efficient collateral circulation may be very soon established, for in Dog 297 the superior mesenteric artery was found completely thrombosed seven days after the operation, though there was no hemorrhagic necrosis of the intestines

Autopsies on the seven dogs that were killed over periods of from three to five months after operation showed that in all cases the organs were normal, except perhaps for some congestion of the liver In two dogs (279 and 288) the bands were found to constrict either the superior mesenteric artery or celiac axis to a considerable degree, though the lumina of both vessels were patent In two dogs (282 and 283) the superior mesenteric artery was completely converted into a fibrous cord and in one dog (290) the celiac axis was completely converted into a fibrous cord, while the lumen of the superior mesenteric artery, though patulous, was narrowed to a pin-hole size An injection of Berlin blue into the femoral artery of one of the dogs in which the superior mesenteric artery was completely thrombosed showed that a free anastomosis had been estab-

lished between the branches of the inferior mesenteric and superior mesenteric arteries The injecting fluid was seen to fill the vessels of the colon in the region supplied by the inferior mesenteric artery, and to pass through into the vessels of the small intestines, coloring the loops of the intestines blue before the stomach and spleen were injected

From these experiments we can conclude, therefore, that extreme narrowing of the mouths of the superior mesenteric artery and celiac axis in dogs is soon compensated for by a collateral circulation so that gradual thrombosis of one or both vessels may take place without serious or obvious detriment to the health of the animal Neither cardiac hypertrophy nor hypertension follows the narrowing of the mouths of these vessels in dogs

Certain criticisms might be offered to such conclusions It is possible that the time elapsing between the operation and the date of death was not sufficiently long to allow for a noticeable increase in the weight of the heart Friedlander,[7] however, has found that in children and young adults hypertrophy may be noticeable four weeks after the onset of acute scarlatinal nephritis, and there is no reason to suppose that hypertrophy may not occur as rapidly in dogs Seven of the dogs were watched at least twice this long, without the slightest evidence of hypertrophy Again it may be said that the condition of the life of these animals after operation was not conducive to hypertrophy, but they were kept under exactly the same conditions as the control dogs and if the operation itself had had any effect on the general vascular system, a comparison with the control dogs should have demonstrated this

We may now ask whether it is justifiable to draw conclusions from these experiments as regards cardiac hypertrophy in man To determine this point, we have examined during the last three years with particular care the condition of the branches of the abdominal aorta at autopsy, and have compared the state of these vessels with the weight of the heart The hearts however have not been weighed by Muller's method but the condition of the organ has been computed by the usual methods During this time we have found forty-six cases (Table 3) in which either the heart showed hypertrophy or the mesenteric artery and celiac axis were narrowed, often to an extreme degree by arteriosclerotic processes, presume from aneurisms or from new growths Naturally all cases in which there was a valvular lesion or disease of the pericardium have been excluded

7 Friedlander Arch f Physiol 1881 165

TABLE 3—CARDIAC HYPERTROPHY AND SCLEROSIS OF ABDOMINAL AORTA

CARDIAC HYPERTROPHY, 37 CASES

Associated with sclerosis of abdominal aorta and narrowing of splanchnic arteries	Chronic nephritis present	10	
	Chronic nephritis absent	2	12
Unassociated with sclerosis of abdominal aorta or narrowing of splanchnic arteries	Chronic nephritis present	20	
	Chronic nephritis absent	5	25
	Total		37

SCLEROSIS OF ABDOMINAL AORTA AND NARROWING OF SPLANCHNIC ARTERIES, 21 CASES

Cardiac hypertrophy	Chronic nephritis present	10	
	Chronic nephritis absent	2	12
No cardiac hypertrophy	Chronic nephritis present	6	
	Chronic nephritis absent	3	9
	Total		21

In this series, shown in Table 3, there were thirty-seven cases of definite cardiac hypertrophy Of these thirty-seven cases twelve or about 32 per cent showed extensive sclerosis of the abdominal aorta with narrowing of the mouths of the splanchnic vessels, or definite stenosis of one or both of the arteries themselves

On the other hand thirty, or 81 3 per cent, were associated with chronic nephritis Of the twelve cases in which narrowing of the splanchnic vessels occurred in combination with cardiac hypertrophy ten, or over 83 3 per cent, showed chronic nephritis and, in the two cases in which there was no nephritis, the hypertrophy was of very slight grade Finally there were nine cases in which narrowing of the superior mesenteric artery and celiac axis occurred in which there was no cardiac hypertrophy demonstrable by the methods employed In five cases, at least the lesion of the abdominal aorta and splanchnic vessels was of a most extreme grade In one instance both vessels were almost occluded by pressure from a new growth in one instance a dissecting aneurism of the celiac axis narrowed the lumen to a mere slit and in three instances there was extreme sclerosis of the abdominal aorta, with much constriction of the superior mesenteric artery and celiac axis Indeed, of the twenty-one cases in which the splanchnic vessels were narrowed only seven were associated with any degree of cardiac hypertrophy and in all seven cases a definite chronic nephritis coexisted

Our experience at autopsy is therefore in accord with that of Marchand,[7] who could find no definite association between cardiac hypertrophy and sclerosis of the abdominal aorta or splanchnic vessels

From these experiments and observations at autopsy it would seem highly improbable that any anatomical lesion of the larger vessels even in the splanchnic area can produce a marked increase of blood-pressure or

give rise to hypertrophy of the heart The gradual narrowing of the vessels which occurs in such a process, even when it is wide-spread, is soon compensated for by collateral anastomoses, so that the distribution of the volume of blood in the body is equalized

That narrowing of the main splanchnic arteries may cause a rise of blood-pressure in any other manner than by shutting off into the general circulation a certain proportion of the volume of blood flowing to the intestines is unlikely from the results of previous experiments on dogs, for it was found that the rise of blood-pressure, following immediately on occlusion of the superior mesenteric artery and celiac axis, was not due to a possible reflex arising from the anemic intestines and causing constriction of the arteries in other parts of the body On the other hand, the excess of blood thrown into the general circulation by this procedure was not sufficiently compensated for by a dilatation of the vessels of other organs, and the general blood-pressure rose, owing to the rapid increase of blood in the general circulation which was not compensated for

Mall[8] has explained the rise of pressure which follows constriction of the splanchnic arteries and, indeed, the mesenteric veins as well, following stimulation of the splanchnic nerves, on the same basis The results of sclerosis of the splanchnic arterioles may be quite different from that of narrowing of the main arteries, but the present investigation is, of course, not concerned with this problem A study, however of the condition of the finest branches of the mesenteric artery is now being made in connection with observations on the blood-pressure during life

CONCLUSIONS

We conclude, therefore, that sudden occlusions of the superior mesenteric artery in dogs results in hemorrhagic infarction of the intestines Permanent constriction of the superior mesenteric artery and celiac axis, as well as gradual occlusion of one or both of these vessels may be present in dogs for at least five months, without giving rise to a definite and constant elevation of blood-pressure or to hypertrophy of the heart

At autopsy, no definite association can be found in man between sclerosis of the abdominal aorta and great splanchnic vessels and cardiac hypertrophy

323 South Sixteenth Street

8 Mall Johns Hopkins Hosp Rep, 1896 1 37, 111

AN INDIVIDUAL QUANTITATIVE INDEX TO TUBERCULIN DOSAGE IN TREATMENT

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Two years ago in a discussion at the National Association meeting,[1] we called attention to the fact that all the surface cells, at least, of the body were in a condition of sensitiveness to the application of the poison which is known to-day as tuberculin, as evidenced by the different methods of tuberculin test which were before the medical profession—the eye reaction, the skin reaction, the urethral reaction, the nasal reaction, etc We urged at that time that, if this were the truth, the discussion as to the methods of diagnosis which had been used were rather futile, that the method should be chosen which was the least dangerous, most ready of application and most easily observed and controlled

A year later we called attention to the necessity of getting away from the qualitative studies of this method of diagnosis, and reducing it to some definite quantitative basis, and offered in an article published[2] in the *Journal of Medical Research,* a definite quantitative plan to be carried out in this test

We do not wish to be accused of entering at this time into a discussion of the value of the cutaneous reaction in diagnosis We feel that it is a point of evidence in diagnosis to be put on the same basis as the clinical thermometer, chest examination, afternoon tiredness, clinical history and all other evidence contributory to the clinical picture caused by the tubercle bacillus It has, however, an especial value in ruling out certain cases as non-tuberculous

At the present time, we feel that on the definite quantitative plan, such as we have suggested it is possible to determine the exact response which the body suffering from tuberculosis will make to definite quantities of tuberculin introduced beneath the skin Here it must be borne in mind that it is just as possible to obtain a constitutional reaction to tuberculin applied by the way of a skin test as it is when the tuberculin is introduced into the body subcutaneously The following is an example

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* A study prepared under the auspices of the Hospital Tuberculosis League of Pittsburg

1 White W C Proc National Assn for the Study and Prevention of Tuberculosis—Discussion—1908 p 96

2 White and Graham Jour Med Research 1909 xx 347

of a fair number of cases which have come under our notice, when the patients have been under the routine hospital supervision of regular temperature registration and personal control, and will serve as a proof of this

On Oct 8, 1909, Mr L was given a skin test on the left forearm 0 01 cm of 100 per cent O T being applied Within an hour reaction had begun, and in twenty-four the reaction was marked, in forty-eight hours very marked, diminishing somewhat in seventy-two hours, the areola remaining, however, for two weeks At the point of inoculation there was marked swelling, heat and redness, and very noticeable redness, swelling and tenderness of the lymphatic leading from the site of inoculation as far up as the axilla For four weeks previous to the skin test the temperature had been normal, except on two or three occasions when it reached 90 F On October 9 at 12 o'clock the temperature was 100 5, at 4, 101, and at 8, 100 5 F On October 10, at 12 o'clock it was 99, at 4, 100, and at 8, 99 F The following day (October 11) the temperature was normal On October 9 the patient complained of weakness, headache and general malaise In fact, there was a good deal of prostration The following day (October 10) he complained of weakness, but the headache was gone and there was only slight general malaise

A year ago, at the meeting of the Association of American Physicians, we read a paper[3] laying down a law of partition of dosage based on the quantitative basis of skin-cell reaction We regret that what should have been termed a preliminary note was published hastily as a paper Certain of the figures given at that time we have since determined to be at fault At the same time we have proved to our satisfaction that the principle contained in that paper is correct, and we wish now to exhibit the result of a year's work which will give the correct partition doses, based on the determination of the minimal cutaneous reaction to definite quantities of tuberculin

REQUISITES IN APPLICATION OF SKIN TEST

We wish first to call attention to certain requisite points which must be carried out in the application of the skin test The tuberculin must undoubtedly be a solution of tuberculin poison such as is contained in the Old Tuberculin or in the filtrate Suspensions of tubercle bacilli such as are contained in the Bazillen-Emulsion and in the T R are not permissible The use of a solution of tuberculin is necessary to render absorption of the poison as easy as possible Suspensions of bacilli containing as they do, clumps of comparatively fair size with the poison still in the bacillary body, do not permit of ready absorption by the lymphatics which is necessary, as will be shown later

The choice of the site for the application of the preliminary skin test is important Many factors enter into this choice first the thickness

3 White, Graham and Van Norman Jour Med Research 1909 xxi, 255

of the cuticle, second, the number and distribution of lymphatics, third, the readiness with which the patient can keep the part at rest until absorption of the solution has occurred, fourth, the absence of hair follicles The thickness of the cuticle varies greatly in different parts of the body, and necessitates, as we have frequently shown in our work, a different depth of scarification to produce the requisites for uniform absorption We have found that the inner side of the forearm has, as a rule, a thin cuticular layer which gives uniform results with approximately the same scarification The distribution of lymphatics in the above location is also fairly uniform, and the channels of lymphatic drainage fairly straight in their course so that in placing tests below one another it is possible, by shifting the lower test to the right or to the left, to obtain a different draining channel from that which is used in the upper test In the matter of keeping the part at rest to allow as complete absorption as possible, no part answers so well as the forearm, which is under the patient's control and not under the necessity of being used, and can be kept in a horizontal position more easily than any other part of the body To fulfil all the conditions outlined, we have chosen the forearm

Preceding the application of the test, to remove any chances of infection, or fat and scurf that may have gathered on the skin, it is best to wipe off the seat of application with alcohol followed by ether

The scarification we consider a point of very great importance The former method, in which we followed Pirquet, was to scarify through the drop of solution This was found to give various results in the same patient at the same and at different times In our present method, we scarify the cleansed skin with such force as just to pierce the upper layer of the cuticle and to elicit a punctate spot measuring 2 mm in diameter, the base of which shows bright pink in color This pink sometimes may not appear for a second or two after the scarification It can be made deeper, if necessary, to accomplish the desired result by waiting a few seconds and watching for the pink appearance It is necessary not to draw the least drop of blood

Objections have frequently been raised to the use of the Pirquet scarifier reasons being advanced in favor of needles and lancets with which are made longitudinal slits in the skin of deeper grade than that obtained by the Pirquet scarifier With none of these however can we agree as it is possible only with the blunt-pointed Pirquet scarifier to obtain a depth and size of scarification which can be readily measured and which will underlie uniformly the measured drop of fluid which we use in this test

The color-index in the way indicated here can be followed more accurately than in any other way which we have tried We have found that only with this color-index can we be sure of having gone the requisite depth at the same and at various times, in the same and in various patients We formerly gave a definite number of twirls with the Pirquet scarifier, but it was found impossible to control this procedure and get the requisite color in different patients, on account of the difference in toughness and thickness of the cuticle

After having made the proper scarification, a drop measuring exactly 0 01 c c of the tuberculin solution to be used is applied by a throttle pipette exactly over the point of scarification This is then covered with a vaccine shield, kept in place by two strips of adhesive, and the patient directed to hold the arm in a horizontal position for at least an hour, so as to prevent flowing of the drop These precautions are necessary, because the essential thing in the tuberculin reaction is the absorption of the poison

PRECAUTIONS IN APPLICATION OF TEST FOR MINIMAL CUTANEOUS REACTION

In the former method of application of this test most of our patients reacted to very much higher percentages of tuberculin than is found with the present method, varying from 1 per cent to 100 per cent of pure old tuberculin The majority of them reacted to 0 01 c c of 12 5 per cent of pure old tuberculin With the present method, when we are sure that all conditions for ready absorption have been fulfilled, the majority of patients react to 1 per cent , very few require as high concentration as 25 per cent , very few of them give a minimal cutaneous reaction to a solution higher than 5 per cent, and many of them react to solutions lower than 1 per cent A fair number give minimal cutaneous reaction with dilutions as low as 0 1 per cent

We would call a minimal cutaneous reaction one that gives redness and swelling measuring 4 to 6 mm in diameter within seventy-two hours Many will object that this is reducing the cutaneous reaction below the point of usefulness, but the longer we work with the cutaneous reaction, the more convinced we become of its absolute specificity and delicate nature, and the more we feel that it is only when under the above precautions one takes into cognizance this delicacy of reaction that one can reach the usefulness to which this method can be put

We now usually begin with a solution of 1 per cent of old tuberculin, because this is the solution to which many of the patients give minimal cutaneous reaction If 1 per cent is found to be too high, as it is in a fair number of cases, one can judge by the size of reaction, and choose the

next best solution to try, reducing it to one-half, one-fourth or one-tenth, as indicated by the size of the reaction If no reaction occurs to 1 per cent solution, one can go to higher concentrations—2, 3, 4 and 10 per cent, as may be indicated by the reaction to the slowly increasing strength of the solution, letting four days elapse between the applications If time is a factor in determining the beginning dose of treatment, one can apply two solutions at the same time on the same arm When time is a factor we frequently use 1 per cent and 0 25 per cent for a first test

Many have objected that one occasionally finds, in obtaining reactions to two solutions of different strengths at the same time, that the area of reaction is greater around the point of application of lesser strength than around the point of application of greater strength This may be true under certain conditions first, that the weaker solution is applied at a point more proximal than the application of the stronger solution, and second, that the application of the proximal weaker solution is along the same lymphatic channel as the more distal stronger solution Under these conditions, as will readily be seen in Figure 1, the lower, stronger solution has drained directly through the lymphatic, which it has definitely reddened, to the point of application of the weaker solution higher up in the same channel, giving a much larger area to the solution above, and then is carried through the lymphatic channel above this, which it has perceptibly reddened in its course It will also be noticed that while the area of redness is greater around the application of the weaker solution, yet the central ulcerated point is much more definite at the site of the stronger solution

Figure 2 shows the result of two tests given at the same time in the correct way, that is, the weaker solution distal and the stronger solution proximal The solutions used in the test shown in Figure 2 were 6 25 per cent (distal) and 12 5 per cent (proximal) O T, and it will be seen that the area of reaction in the proximal is about twice the size of the area of reaction of the distal test with weaker solution A corresponding result is seen in Figure 3 in which 0 1 per cent and 0 25 per cent O T were used

So far as we have been able to find the question of the importance of the lymphatics and the redness of the lymphatic channels produced by the application of the tuberculin skin test has never before been brought to the attention of the profession

The next illustration (Fig 4), which has been taken directly from the arms after the applications of varying strengths of solution will at once convey the truth of the statement that the lymphatic vessels bear a very striking and important part in this reaction and will give the proof

of the necessity which is required for allowing for the period of more complete absorption of the poison from the point of application, and we would emphasize again that, when two applications of tuberculin are made at the same time, the greatest care must be exercised not to place them in such a way as to allow drainage from them along the same lymphatic channel This undoubtedly explains the variations of reaction to different strengths of solution which are found in the published photographs of Pirquet and others

We feel that the question of lymphatic distribution is a point which must be borne very strictly in mind in treatment with tuberculin, the focal reaction around the tuberculous lesion being a requisite factor in treatment The dose in treatment may be so given as to drain along the lymphatic into the site of the lesion, and thus obtain the benign influence of focal reaction This would apply to glands, sinuses, bone lesions and lupus

We would emphasize also this second point, namely, that, in making two applications at the same time, the precautions must always be observed of placing the weaker solution at a point distal to the stronger solution We feel that, only under the most pressing necessity should two tests on which a dosage is to be determined ever be given at the same time

When these precautions are observed in the application of the test to determine the minimal cutaneous reaction, we feel that results directly comparable with our own will be obtained

We must, however, further indicate certain precautions that are necessary to observe in determining the minimal cutaneous reaction, from certain phenomena which have arisen which evidence the vigor of the body cells of the patient to whom the test is applied We formerly thought that the vigor of the body cells had much to do with the intensity of reaction, having found certain patients who, though they had a lung lesion on physical examination of a first or second stage Turban, with tubercle bacilli in the sputum, did not react to 100 per cent Old Tuberculin given repeatedly, but who later reacted to a lower percentage after much improvement in general condition and body weight had taken place We afterward determined that this depended almost, if not wholly, on the depth of scarification, and when we applied the above-outlined method of deep scarification, being sure to pierce the cuticle these cases were reduced to a minimal cutaneous reaction of 0 01 cc of a varying percentage from 0 1 per cent to 10 per cent In fact, so striking has this been in the reaction of patients, when the precaution as to depth of scari-

fication is taken, that we have come to look on the scarification as the most important part of the technic

It has been urged that a part of the skin which has formerly responded to an application of tuberculin by the signs of redness, tenderness and swelling will not react to a later application of tuberculin within a given period of time This, however, we have proved to be a fallacy, as the same spot will react again to further applications of the same strength of tuberculin, or a lower strength of tuberculin, within at least two months of the time of the application of the test, as is shown in Figure 5

A caution must here be added on the point of persistence of the sensitiveness to the same strength of tuberculin application In the hospital many patients who have received tuberculin regularly for a year or more under the method outlined have not changed in their sensitiveness to tuberculin used as a skin test

We feel that in the past a grave mistake has been committed in confusing susceptibility to tuberculin with the sensitiveness which is produced by the growth of the tubercle bacilli in the living body All that can be said at the present time is that sensitiveness of the cells of the body to tuberculin is due to the growth of the tubercle bacilli in the living human body, and we have not yet been able to secure undoubted evidence that any increase of sensitiveness has been aroused in the body, in which the tubercle bacilli have grown, by the use of tuberculin We shall discuss this point in a later paragraph in this paper, but wish to call attention to it at the present time

Cases which have formerly been described as being hypersensitive to tuberculin, we feel, can all be explained on the basis of the degree of sensitiveness present in the first instance, as indicated by our cases which react to percentages as low as 0 1 per cent Almost any of the doses of Old Tuberculin formerly given would have produced some degree of reaction in these patients, but, their sensitiveness having been determined by our method, it is possible to give such minimal doses as to avoid the reaction produced in these cases when treated by the former method of administration The same argument is applicable to those cases of so-called hypersensitiveness after subcutaneous administration of tuberculin for constitutional reaction in diagnosis

THERAPY OF TUBERCULIN REACTION

In discussing the therapy of tuberculin reaction it is necessary to bear in mind three factors, the cells, the serum, and the tuberculin poison, and the interaction of each of these three factors on the two others of the group All of these relations we do not pretend to have worked out but,

as a proof of the influence of the serum it may be well to interject here a note on certain studies which we have carried out in relation to the neutralization power of serum on tuberculin in the cutaneous test[4] In these studies we found one group of patients in whom the serum added to tuberculin was able to augment the reaction In studying this group during the past year, we have found that the serum of one patient is able to produce a cutaneous reaction in patients who react to 0 1 per cent O T as is shown in Figure 6 We were able to obtain the reaction in two cases first, in the patient whose serum was used and whose minimal cutaneous reaction is 0 5 per cent, that is, this patient reacted to his own serum, second, in a patient whose minimal cutaneous reaction is 0 1 per cent The reaction in this patient is shown in Figure 6

Just what the bearing of this is and how frequently it occurs, we are not prepared at this time to state, but in this patient it had no relation to tuberculin administration, either for treatment or for skin testing, and the only factor that we were able to determine, which might have a bearing, was that the patient at the time had a mild fever, but in trying the serum of other advanced cases with fever there was no reaction produced even on the skin of those patients who were most acutely sensitive to tuberculin

TABLE 1.—QUANTITY OF TUBERCULIN (O T) USED IN CUTANEOUS TEST OF VON PIRQUET

Dose in c c	Concentration of Solution %	Quantity in mg of O T Applied
0 01	0 1	0 01
0 01	0 25	0 025
0 01	0 5	0 05
0 01	1	0 1
0 01	5	0 5
0 01	10	1
0 01	20	2
0 01	50	5
0 01	100	10

Having stated these precautions and with these preliminary remarks, we can now take up the question of therapeutic doses of tuberculin which can be given on the minimal cutaneous reaction basis From the table of quantities of tuberculin contained in the various dilutions of tuberculin (Table 1) it will be seen that the most important point in determining the dose to be given for therapeusis, is the use of 0 01 c c of tuberculin in the skin test, which gives a definite quantity of tuberculin on which to base a partition dose in the matter of treatment As outlined in our former paper, we suggested that there was a definite relation between the

4 White and Graham Jour Med Research, 1909 xxi, 261

quantity of tuberculin which produced a certain amount of reaction on the skin and the amount of tuberculin which, given under the skin, could produce varying grades of reaction from a slight local to a maximum constitutional and focal reaction in the individual

In the former paper we made the statement that "one-fifteenth of the amount of O T, which, when applied to the skin by our method, produced the minimal cutaneous reaction, would, when given subcutaneously, produce both local and constitutional reactions, that one-thirtieth of the same amount given subcutaneously would produce local without constitutional reaction Later work has shown that one-fiftieth of the minimal cutaneous reaction dose will produce neither local nor constitutional reactions when given subcutaneusly" These figures, we must now state, were not correct, but this was mainly due to the fallacy of our method in applying the skin test, which we have since corrected, as outlined in the first part of this paper

The past year's work has determined, however, that the quantity of tuberculin contained in 0 01 c c of that definite solution of tuberculin which will produce exactly the minimal cutaneous reaction, which we have arbitrarily called 4 to 6 mm redness and swelling at the site of application of the test, will produce, when given underneath the skin, an area of redness, tenderness and swelling measuring from 2 to 5 cms From observation on a very few cases it would seem that, if this dose is increased ten times, it will produce the symptoms of constitutional reaction, and if it be reduced in amount to one-tenth, it will be below the amount which will produce even a local reaction at the site of inoculation We have, however, not yet been able to verify these last two figures in a sufficient number of cases

In determining the dose on the skin test, and to show how sensitive is its individual biological basis, and how important are the measurements in millimeters which we have outlined, we would cite an individual case representative of a large class

Mr A reacted to a 5 per cent solution of O T giving an area of redness of 13 by 9 mm in forty-eight hours Four days later 3 per cent was given, causing a reaction of 9 by 8 mm in forty eight hours Five days later 2 per eent was given, the resulting reaction being 8 by 7 mm in forty-eight hours Four days later 1 per cent was given, the reaction being 7 by 5 mm in forty eight hours Four days later 0 25 per cent was given In twenty-four hours there was slight redness of 2 mm at the point of inoculation but this had faded in forty-eight and seventy two hours Four days later 0 5 per cent was given, the resulting reaction being 4 mm in forty-eight hours

It will be seen, therefore that in order to make this arbitrary law applicable, it is absolutely necessary to obtain that quantity of tuberculin which will produce exactly a minimal cutaneous reaction of 4 to 6 milli-

meters, in order to say that the same quantity introduced under the skin will produce redness of 2 to 5 centimeters

Much of our original discrepancy came from guessing at the quantity of tuberculin to be given therapeutically on the basis of a result from two solutions

An example would be as follows A case would be given 5 per cent as the initial skin test, the reaction being about 1 cm Five days later 0 5 per cent would be given, with no reaction Formerly we would have guessed the basis to be 3 per cent, whereas, there would likely have been a reaction of 4 or 5 mm to a 1 per cent solution

In determining the minimal cutaneous reaction it is necessary to watch the reaction at the end of twenty-four, forty-eight and seventy-two hours Oftentimes at the end of twenty-four hours there is an outer ring of faint pinkness around the red reaction This pink often fades at the end of forty-eight hours, and it must not be taken into account in the measurement of the minimal reaction (central redness) Occasionally the reaction, as has been observed by many other writers, is delayed at least forty-eight hours, and it may be as late as seventy-two, or even later The redness around the control scarification disappears before forty-eight hours while the redness of reaction persists, often for weeks Our method of registering the minimal cutaneous reaction can be seen by Table 2

TABLE 2—SKIN TESTS

Patient	Date, March	Percentage of Tuberculin	Result * In 24 Hours,	In 48 Hours,	In 72 Hours	
Miss E	7/10	1	5× 5↑	5× 5↑	5× 5?	M C R
Miss J	7/10	0 5	5× 4‡	2 ↑		M C R
Mr A	7/10	0 25	6× 6+	4× 4+	4× 4?	M C R
Mrs B	7/10	0 1	5× 3‡	6× 4↑	5× 4↑	M C R
Mr C	15/10	1	7× 7+	5× 5+	5× 5↑	M C R=0 7 %
Mr C	20/10	0 5	5× 4+	4× 4+	4× 4‡	
Mr C	25/10	0 25				
Mrs D	15/10	2	1 3× 5+	1 5× 1+	1 0× 8‡	M C R=0 5 %
Mrs D	20/10	1	9× 6+	1 3× 8‡	1 0× 7‡	
Mrs D	25/10	0 5	6× 6‡	4× 4+	4× 1↑	
Mrs D	30/10	0 25				

* Figures = diameter (in centimeters) of areola of reaction, ? = very slight redness of areola ↑ = slight, ‡ = moderate, + = marked, M C R = minimal cutaneous reaction

Having determined the dose of tuberculin which will produce underneath the skin an area of redness and swelling measuring 2 to 5 cm

Fig 1—Showing the reaction after application of 25 per cent old tuberculin at the distal point and 6 25 per cent at the proximal point The reaction around the application of 6 25 per cent solution is greater than that around that of 25 per cent Note the reddened lymphatic

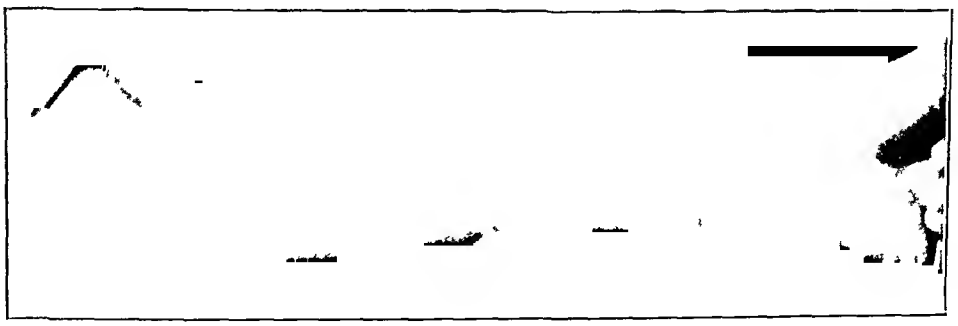

Fig 2—Showing definite quantitative response to solutions of varying strength The strength of the distal solution is one half that of the proximal solution, and the response approximately one half

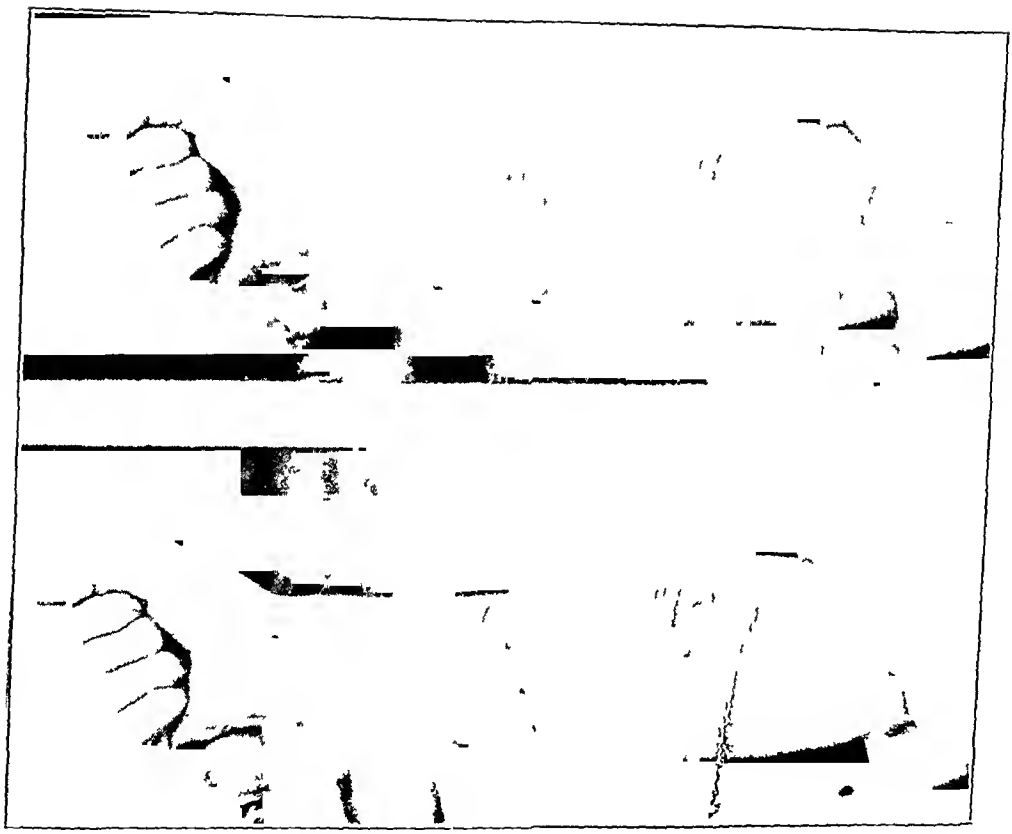

Fig 3—Similar to Figure 2 It also shows shifting of the distal point of application to the ulnar side to avoid the same lymphatic drainage as that of the proximal solution

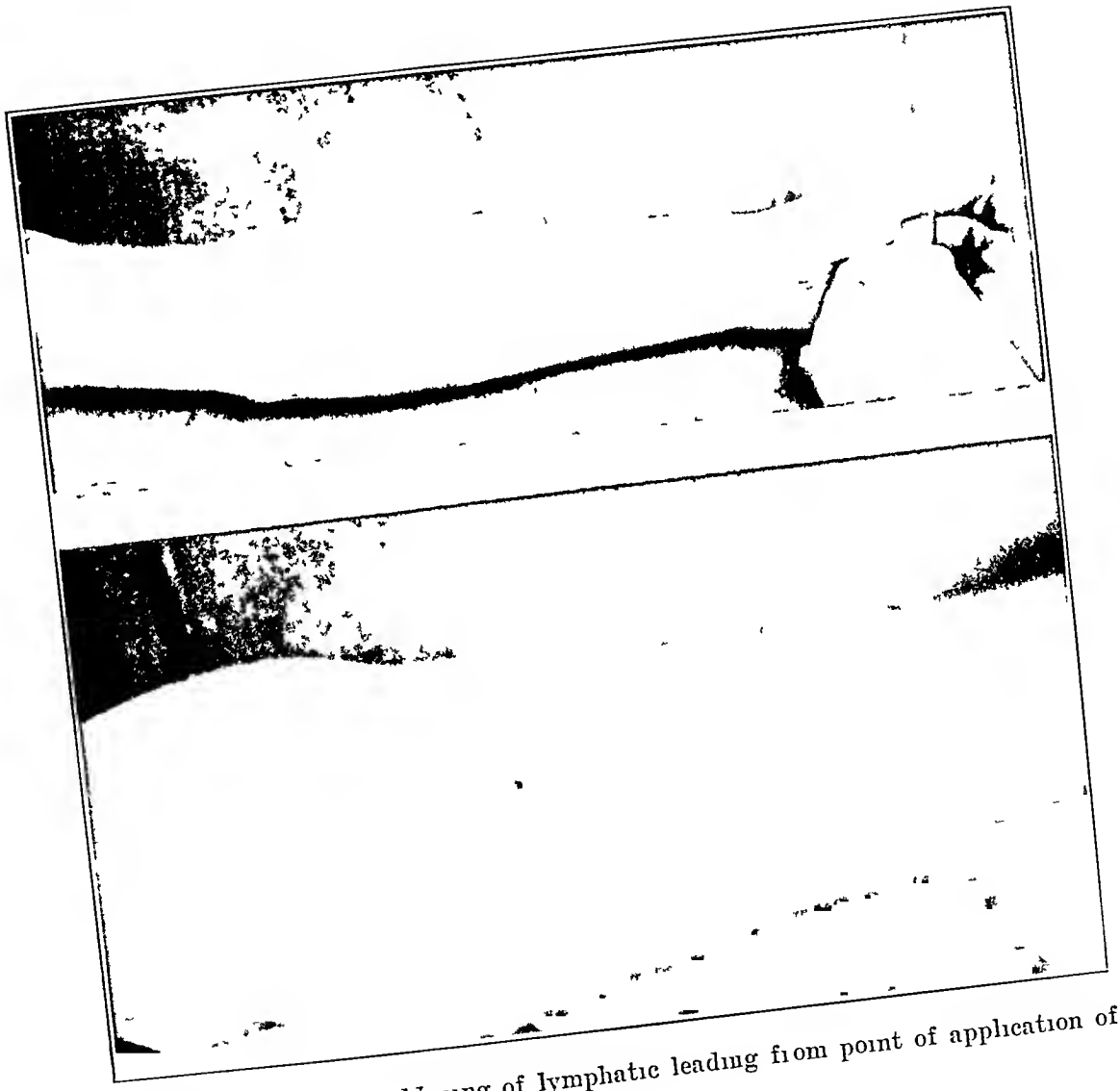

Fig 4 —Showing reddening of lymphatic leading from point of application of tuberculin

Fig 5—Showing reaction of the application of 1 per cent old tuberculin to points which previously reacted to 6 25 per cent and 25 per cent old tuberculin These tests were applied to the same spots as shown in Figure 1

Fig 6—Reaction to serum of patient whose serum augmented tuberculin reaction Notice also lymphatic redness

which is, as stated above, the quantity of tuberculin which is contained in 0 01 c c of the solution of tuberculin which produces a minimal cutaneous reaction measuring 4 to 6 mm , we must next approach the question of what is the desirable therapeutic dose, and the method of procedure for future dosage

The first question that may fairly be asked is, whether or not we have proof that tuberculin is a valuable therapeutic agent This can undoubtedly be answered in the affirmative, as everyone who has used tuberculin must have concluded, from its action on bone and gland sinuses, localized tuberculous lesions in glands and various organs (especially would we call attention to certain corneal ulcers), and from its application in lupus These give, without question, a positive answer to the value of tuberculin in treatment

The next point to be determined is what dose of tuberculin is the valuable dose There has been a marked variance of opinion between the German and English investigators in this matter The German investigators have recently been tending towards the administration of doses large enough to produce constitutional reaction The English observers have tended towards exceedingly small doses, guided in their therapy by the opsonic index method as indicated by Wright In this country the English method of small doses has mainly been followed in an outline laid down by Trudeau and Brown of Saranac Lake It must have struck most observers who formerly gave tuberculin subcutaneously that patients seemed to improve very markedly in general feeling and in diminution of sputum and often of fever after a constitutional reaction such as was obtained in the former method of diagnostic administration of tuberculin

Too much importance cannot be laid on Dr Trudeau's experiments[5] in the tuberculous eyes of rabbits, which were given tuberculin in sufficient doses to produce focal reaction, and which local eye lesions made marked improvement following the reaction Saathoff[6] has recently called attention to this fact in a paper from Muller's clinic, in which he was able to watch a corneal lesion improve steadily after the repeated focal reactions produced by the tuberculin administration Dr Trudeau[7] remarks in a paper published a year ago that "improvement in the lesion may depend on the influence of these mild reactions, but in considering the advisability of utilizing mild, general and focal reactions as a feature

5 Trudeau, E L Tr Assn Am Physicians, May 24, 1892

6 Saathoff Munchen med Wchnschr , 1909, lvi, 2041

7 Trudeau, E L Antibacterial or Antitoxic Immunity in Tuberculin Treatment, Jour Am Med Assn , 1909, lii, 61

of treatment, we must not forget that we have no means of controlling the severity of these reactions and that violent reactions are not without danger"

We have been struck with the apparent uselessness of giving small doses of tuberculin in pulmonary and gland tuberculosis, which types of cases mainly have been under our supervision For two years we followed the method of administration of tuberculin by small doses repeated frequently, and we have at the present time under our care patients who have been receiving tuberculin in this hospital for a period of three years or more During the first two years of their stay in the hospital they received tuberculin by small, frequently repeated doses, and apparently made no marked improvement other than would be looked for from hygienic conditions During the past year, however, when they have been treated with doses which produce mild reactions below the fever line, they have made great and noticeable strides, while in the months previous they had been practically at a standstill It may be objected to this, of course, that tuberculosis takes a wave-like course, but we feel that this is not a valid objection, when the condition has steadily improved with an increased feeling of well-being and diminution of sputum after each local reaction produced by the tuberculin dose In some of these cases the sputum has diminished to one-half or one-third of the former quantity

It may be best here, without further discussion, to say that we believe, first, in doses that will produce mild reactions below the fever line in all cases of tuberculosis that admit of tuberculin as a therapeutic agent, second, that the thing to be obtained is the reaction of the cells and not the tolerance to the tuberculin poison We have come to look arbitrarily on the reaction of greatest good as one which will produce underneath the skin an area of redness, tenderness and swelling of approximately 2 to 5 cm in diameter at the site of injection We have not seen a single case to shake our faith in this basis of dosage in the administration of over one thousand injections of tuberculin for therapy, based directly on the minimal cutaneous reaction

The next point of importance is the spacing of the dosage We have found that tolerance to tuberculin can readily be established if the doses are given in the Saranac method three or four days apart and in increasing doses On the other hand, we have found that, as a rule, when once the dose which will produce the above degree of redness at the site of injection based on the minimal cutaneous reaction has been determined, that patients retain, as a rule the same degree of reaction for periods reaching as high as nine months The cases summarized in Tables 3 and 4 illustrate this point·

TABLE 3—SHOWING UNIFORMITY OF LOCAL REACTION FROM SAME DOSE OF TUBERCULIN *

Date	Tuberculin, O T	In 24 Hours: Local Redness, cm	Local Tenderness	Local Swelling	In 48 Hours: Local Redness cm	Local Tenderness	Local Swelling	Constitutional Symptoms
8/15/09	0002	2			3			—
8/25/09	0002	2			5+	+		—
9/ 4/09	0002	3			4	+		—
9/14/09	0002	3			3	+		—
9/24/09	0002	2			4	+		—
10/ 4/09	0002	2			3	+		—
10/14/09	0002	2			4	+		—
10/24/09	0002	2			2 5	+		—

* Significance of characters same as in Table 1

TABLE 4—SHOWING UNIFORMITY OF LOCAL REACTION FROM SAME DOSE OF TUBERCULIN DURING EIGHT MONTHS *

Date	Tuberculin, O T	In 24 Hours: Local Redness, cm	Local Tenderness	Local Swelling	In 48 Hours: Local Redness cm	Local Tenderness	Local Swelling	Constitutional Symptoms
8/ 3/09	0001	2 5			2 5			—
8/25/09	0001	2 5			2 5			—
9/27/09	00015	4 +	+	+	4 +	+		—
10/28/09	0001	2 5			2 5			—
11/ 8/09	0001	3			3			—
11/18/09	0001	2			5			—
11/29/09	0001	3			3			—
1/29/10	0001	3	+	+	6		+	—
2/12/10	0001	5	+		3	+		—
2/28/10	0001	3	+		3	+		—
3/14/10	0001	3			4			—
4/ 4/10	0001	3×2			5×4+			—

*Significance of all characters same as in Table 3

Consequently, having determined to our own satisfaction that patients do better when they retain their reaction to tuberculin, we feel that it is infinitely better to continue the same dose with an interval of fourteen days between doses A word of caution must be added here, namely, that a skin test, with the readiness with which tuberculin is absorbed, is equivalent to a therapeutic dose of tuberculin and, if the first dose of tuberculin for therapy be given within a few days after the exhibition of a skin test, the resulting local reaction at the point of injection is apt to be greater than if the injection of the therapeutic dose is delayed fourteen days

The choice of the site of injection of the therapeutic dose of tuberculin is not apparently a matter of great importance, as we have determined without failure up to the present time that the same dose of tuberculin given in either arm, leg or trunk produces approximately the same degree of redness and tenderness

A word or two here in reference to the technic of administering tuberculin might not be amiss We have already mentioned that, whether the tuberculin be given in the legs, arms or trunk, one always gets approximately the same amount of redness and tenderness with the same dosage As a rule, however, in tuberculin treatment, we begin by using the arms, each arm being used alternately The tuberculin is administered in the arm between the shoulder and elbow on its posterior aspect that is, over the triceps muscle It should be given just under the skin and not injected deeply The skin is cleansed with alcohol, and is then pinched up ready for the plunge of the needle, which is inserted with the bevel-edged opening pointing outward towards the skin surface In order to give the tuberculin subcutaneously, the needle is entered through the skin at a very acute angle, and it is advisable to insert it up to the hilt, so that when it is withdrawn no tuberculin will exude through the opening The reason for keeping the beveled edge of the needle outward is that the tuberculin when leaving the needle may enter the cutaneous tissue, and not the deeper tissues, for, if the tuberculin be injected deeply into the tissues, the resulting local reaction may be much less than when the tuberculin is given just under the skin, and to a certain extent one judges the dosage of the tuberculin by the amount of local reaction After using the arms for a few injections, one may give the tuberculin in the thighs, back, chest or abdominal wall

It may now be asked what advantage there is in determining a dose of tuberculin on the basis of a minimal cutaneous reaction, if one does not desire to obtain the reaction produced by tuberculin of the degree indicated in this paper The method suggested here is not directly applicable save by those who believe in local reaction At the same time it will allow the determination of a perfectly safe dose, varying at least 100 per cent in quantity According to our studies we have determined that in tuberculin dosage there is in individuals a variation of the primary dose from at least 0 000005 to 0 0005 mg of tuberculin, to produce the same amount of reaction, that is, this method is capable of giving at once an initial dose of tuberculin varying from 0 000005 to 0 0005 mg of O T — a dose varying one hundred times in amount from the smallest to the largest This forms then a basis for dosage vastly in advance of the former method when all patients were given doses of tuberculin of

minimal amount in gradually increasing quantities until the point of reaction was reached In this way it is possible to determine a dose for each case which will produce exactly the same degree of local reaction in all individuals

TABLE 5—SHOWING RELATION BETWEEN MINIMAL CUTANEOUS REACTION AND THERAPEUTIC DOSE OF TUBERCULIN

Minimal Cutaneous Reaction % O T	Therapeutic Dose mg O T
0 05	000005
0 1	00001
0 25	000025
0 5	00005
0 75	000075
1	0001
2	0002
3	0003
4	0004
5	0005
6	0006
7	0007
8	0008
9	0009
10	001

Instead of taking, as in former instances, three, four or five months to reach a dose such as is indicated here it is possible to reach it within three weeks' time, so that, if there were no gain in the reaction, at least there is a great gain in arriving quickly at the individual dose which the patient can tolerate We feel that the greatest gain, however, comes in determining the quantity of tuberculin which will give a mild reaction in every individual, and it is only when we get a dose of tuberculin which will produce these mild reactions that we can hope for beneficial results of a curative nature

We feel that we have offered for the first time in therapy a specific, individual, biological test for therapeutic doses which is, of course, the goal to be aimed at in all therapeutic measures In other words, instead of giving a dose of a drug which is known to produce a certain physiological effect, in a small number of individuals, it is possible in this way to give exactly the dose of the drug which is best suited to each individual, and this must, in future, be the basis of rational therapeutics

We are unfamiliar at this time with the causative factors which vary the sensitiveness of the body cells to tuberculin, but we would here add a closing caution that, if sometimes during tuberculin therapy the sensitiveness of the body to the tuberculin changes, it is best to determine the minimal cutaneous reaction before giving another therapeutic dose In

this way it will be possible to keep the body at about the same reaction to therapeutic doses of tuberculin

We have found that, as a routine practice, it is well to repeat the skin test for minimal cutaneous reaction every three months, but in pursuing this course, we have come to the conclusion that it is not the tuberculin administered which changes the susceptibility to this poison, but some deeper and more subtle influence

CONCLUSIONS

1 It is just as possible to obtain a constitutional reaction from tuberculin placed on the skin as from tuberculin introduced beneath the skin Tuberculin reactions, whether local, focal or constitutional, must be looked on as varying grades of the same response of the body to a varying quantity of tuberculin used

2 In the body in which tuberculosis has developed, the degree of reaction of the surface cells to the poison contained in the different tuberculins depends on (a) depth of scarification, (b) point of application, (c) distribution of lymphatics, (d) readiness of absorption, (e) exact amount of tuberculin used

3 At times the serum of individual cases contains a substance which is capable of producing a cutaneous tuberculin reaction in individuals who are very susceptible to tuberculin

4 The interval of dosage varies for the result desired, less than seven days for tolerance, and fourteen or more for retention of the reaction power of the cells

5 In the majority of patients, if the interval of doses be two weeks or more, the amount of local reaction from the same dose of tuberculin does not change in a period of many months

6 It is possible by determining the minimal cutaneous reaction to 0 01 c c of varying solutions of tuberculin, to state the exact amount of tuberculin which will produce a certain grade of reaction when introduced beneath the skin

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